EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 May 2021
EMA/394228/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Verquvo

International non-proprietary name: vericiguat

Procedure No. EMEA/H/C/005319/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Verquvo
Applicant:	Bayer AG Kaiser-Wilhelm-Allee 1 51373 Leverkusen GERMANY
Active substance:	VERICIGUAT
International Non-proprietary Name/Common Name:	vericiguat
Pharmaco-therapeutic group (ATC Code):	(C01DX22)
Therapeutic indication(s):	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 (see section 5.1).
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	2.5 mg, 5 mg and 10 mg
Route(s) of administration:	Oral use
Packaging:	blister (PP/alu), blister (PVC/PVDC/alu) and bottle (HDPE)
Package size(s):	10 x 1 tablets (unit dose), 100 x 1 tablets (unit dose), 14 tablets, 28 tablets, 98 tablets and 100 tablets

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List of abbreviations

AAS	Atomic Absorption Spectrometry
ADP	Adenosine diphosphate
ADME	absorption, distribution, metabolism and excretion
AE	adverse event
AF	atrial fibrillation
AHU377	Sacubitril
ANCOVA	analysis of covariance
ANDA	Abbreviated New Drug Application (ANDA) is an application for a U.S. generic drug approval
ANP	Atrial natriuretic peptide
AP	Applicant's Part (or Open Part) of a ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ARB	Angiotensin II receptor blocker
ASA	acetylsalicylic acid
ASM	Active Substance Manufacturer
☐ SMA	Alpha-smooth muscle actin
ASMF	Active Substance Master File = Drug Master File
AUC	area under the curve
AUC_t	AUC for the actual dose interval
AUCnorm	AUC divided by dose per body weight
AUCu,norm	AUC unbound divided by dose per body weight
$BaSO_4$	Barium sulfate
BCS	Biopharmaceutical Classification System
bid	bis in die (twice a day)
BNP	B-type natriuretic peptide
BP	Blood pressure
bpm	Beats per minute
BRCP	breast cancer resistance protein
CAD	coronary artery disease
CBF	Coronary blood flow
CEP	Certificate of Suitability of the EP

CFU	Colony Forming Units
cGMP	Cyclic guanosine monophosphate
CHO	Chinese hamster ovary
CI	confidence interval
CKD	chronic kidney disease
CL/F	apparent clearance
CLCr	creatinine clearance
CLR	renal body clearance
Cmax	Mean maximum drug concentration in plasma
Cmax,u	Maximum concentration of unbound fraction
C-QTc	concentration-QTc modeling
Ctrough	concentration at trough
CMS	Concerned Member State
CNS	Central nervous system
CO	Cardiac output
CoA	Certificate of Analysis
CRS	Chemical Reference Substance (official standard)
CV	coefficient of variation
CV	cardiovascular
CVP	central venous pressure
DBP	diastolic blood pressure
DDI	drug-drug interaction
DEA/NO	Diethylamine/nitric oxide complex
DMSO	Dimethylsulfoxide
+dP/dt	Left ventricular contractility
DoE	Design of experiments
DP	Decentralised (Application) Procedure
DPM	Drug Product Manufacturer
DSC	Differential Scanning Calorimetry
EC50	Median/half maximum effective concentration
ECG	Electrocardiogram
ECI	events of clinical interest
EDQM	European Directorate for the Quality of Medicines

e.g.	exempli gratia, for example
EP	European Pharmacopoeia
F	bioavailability
FCR	Functional Related Characteristics
FPM	Finished Product Manufacturer
fu	fraction unbound in plasma
GC-A	Receptor guanylyl cyclase GC-A
GC-B	Receptor guanylyl cyclase GC-B
geoCV	geometric coefficient of variation
GLP	Good Laboratory Practice
GTN	Glycerol trinitrate
GTP	Guanosine triphosphate
h	Hour(s)
HCT	Hydrochlorothiazide
HDPE	High Density Polyethylene
HEK	Human embryonic kidney
hERG	Human Ether-à go-go Related Gene
HF	Heart failure
HFrEF	HF with reduced ejection fraction
HR	Heart rate
HR1min	heart rate over 1 minute
HT	Holding time
IC20	Concentration required for 20% inhibition
IC50	Median/half maximum inhibitory concentration
ICH	International Council for Harmonization
i.e.	id est, that is
IPC	In-process control
IR	Infrared
IR	immediate release
ISMN	isosorbide mononitrate
IU	International Units
IV	Intravenous
IIV	interindividual variability

ka	absorption rate constant
kg	Kilogram
K+	Potassium ion
LDPE	Low Density Polyethylene
L-NAME	L-nitroarginine methyl ester
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantitation
LoQ	List of Questions
LT	Less than
LVP	Left ventricular pressure
LVEDP	Left ventricular enddiastolic pressure
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MAP	Mean arterial blood pressure
md	multiple dose
MEB	Medicines Evaluation Board
MS	Mass Spectrometry
MEC	Minimum effective concentration
mg	Milligram
min	Minute(s)
mmHg	Millimeter of mercury
µg	Microgram
µM	Micromolar
MOA	mechanism of action
MRT	mean residence time
ND	Not detected
NEP	Neutral endopeptidase, Neprilysin
NLT	Not less than
nM	Nanomolar
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NO	Nitric oxide

NTG	nitroglycerin
NT-proBNP	N-terminal peptide sequence of the brain natriuretic peptide prohormone (proBNP)
OATP1B1	organic anion transporting polypeptides
OATP1B3	organic anion transporting polypeptides
OCP1	organic cation transporter 1
ODQ	1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one
OECD	Organisation for Economic Co-operation and Development
OOS	Out of Specifications
p	Statistical significance
PAP	Pulmonary artery pressure
PBS	Phosphate buffered saline
PBPK	physiology-based pharmacokinetic
PD	pharmacodynamics
PDE	Permitted Daily Exposure
PDE 5	phosphodiesterase type 5
PDS	pharmacodynamic analysis set
PE	Polyethylene
PEG	Polyethylene glycol
P-gp	P glycoprotein
Ph. Eur.	European Pharmacopoeia
PH-LVD	Secondary pulmonary hypertension
PIL	Patient Information Leaflet
PK	pharmacokinetics
PKS	pharmacokinetic analysis set
PO, p.o.	Per Os, oral
pop	population
PP	Polypropylene
PQ	PQ interval in ECG
PRP	Platelet-rich plasma
PT	prothrombin time
PTF	peak trough fluctuation
PTZ	Pentylenetetrazol
PVC	Poly vinyl chloride

PVR	Pulmonary vascular resistance
Qd/QD	quaque die, once daily
QOS	Quality Overall Summary
QRS	QRS complex in ECG
QT	QT interval in ECG
QTc	corrected QT interval in ECG
QTcB	QT interval frequency-corrected according to Bazett's formula
QTcF	QT interval frequency-corrected according to Fridericia's formula
R_AAUC	AUC accumulation ratio
R_ACmax	observed peak concentration accumulation ratio
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of an ASMF
RRT	Relative retention time
RSD	Relative standard deviation
RV	residual variability
SBP	Systolic blood pressure
SD	standard deviation
SEM	Standard error of mean
sGC	Soluble guanylate/guanylyl cyclase
SHR	Spontaneously hypertensive rats
SIN 1	Linsidomine
sLVP	Systolic left ventricular pressure
SMA	Smooth muscle actin
SNAP	S-nitroso-N-acetyl-D,L-penicillamine
SNP	Sodium nitroprusside
SPC	Summary of Product Characteristics
SoE	Summary of effect
SVO2	Oxygen saturation in the coronary sinus
SVR	Systemic vascular resistance
TEAEs	treatment-emergent AEs
TGA	Thermo-Gravimetric Analysis
tmax	Time to reach maximum drug concentration in plasma

TRAP-6 Thrombin Receptor Activator Peptide 6

U 46619 9,11-dideoxy-9□,11□-methanoepoxy prostaglandin F2□

Unc Uncertainty

USP/NF United States Pharmacopoeia/National Formulary

UV Ultraviolet

VASP Vasodilator-stimulated phosphoprotein

Vc/F apparent central volume of distribution

vs Versus

Vz/F apparent volume of distribution

XRD X-Ray Diffraction

BCS Biopharmaceutics Classification System

CQA Critical quality attribute

DMF N,N-Dimethylformamide

DoE Design of experiments

EC European Commission

EU European Union

FMEA Failure mode effects analysis

GC Gas chromatography

HDPE High density polyethylene

HPLC High performance liquid chromatography

HRMS High resolution mass spectrometry

ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICP-MS Inductively coupled plasma - mass spectrometry

IR Infrared

IR-ATR Infrared – attenuated total reflectance

KF Karl Fischer titration

LDPE Low density polyethylene

NMR Nuclear magnetic resonance

OFAT One factor at a time

PDE Permitted Daily Exposure

Ph. Eur. European Pharmacopoeia

PP Polypropylene

PVC Polyvinyl chloride

PVDC	Polyvinylidene chloride
QbD	Quality by design
QC	Quality control
QTPP	Quality target product profile
RH	Relative humidity
SmPC	Summary of product characteristics
TSE	Transmissible Spongiform Encephalopathy
UV	Ultraviolet
UV-VIS	Ultraviolet-visible
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bayer AG submitted on 27 May 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Verquvo, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 February 2019.

The applicant applied for the following indication

Verquvo is indicated for the treatment of symptomatic chronic heart failure in adult patients with ejection fraction less than 45% who had a previous worsening heart failure event (see section 5.1).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0070/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0070/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active substance status

The applicant requested the active substance vericiguat contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	
28 January 2016	EMEA/H/SA/3216/1/2015/III	

The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Starting material for the drug substance. Raw materials in the synthesis of the drug substance.
- Adequacy of the completed and proposed non-clinical studies to support a MAA.
- Adequacy of the completed, ongoing and proposed clinical pharmacology studies to support a MAA. Design of the single pivotal Phase III HFrEF study including: dose and titration scheme; the primary composite efficacy endpoint (time to CV death and first HF hospitalization) and secondary endpoints; inclusion and exclusion criteria; the definition/use of standard of care; acceptance of a single pivotal trial in support of MAA; inclusion of an enriched high-risk CHF population and implications for the indication; protocol procedures associated with patients within the lower BP range (100 < 110 mm Hg); statistical analyses including stratification, subgroup analysis, handling of missing data, sample size calculation and a proposed interim analysis for efficacy.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Alar Irs

The application was received by the EMA on	27 May 2020
The procedure started on	18 June 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	7 September 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	9 September 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	18 September 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 October 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 January 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	02 March 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	25 March 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 April 2021

The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	04 May 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Verquvo on	20 May 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant is proposing the following 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 (see section 5.1).

2.1.2. Epidemiology

Heart failure (HF) is a major global health concern. The incidence of heart failure in Western countries is between 5 and 10 per 1,000 person-years. In developed countries, the prevalence of HF is approximately 1-2 % of the adult population, rising to up to 10% in people aged> 70 years. It is estimated that more than 60 million patients worldwide have HF (GBD 2016 Collaborators (Disease and Injury Incidence and Prevalence) 2017). Across Europe, fifteen million individuals have been reported to have HF (Benjamin et al. 2019, Dickstein et al. 2008).

2.1.3. Biologic features, aetiology and pathogenesis

Impairments in the nitric oxide- soluble gyanylate cyclase- cyclic guanosine monophosphate (NO-sGC-cGMP) signaling pathway contribute to disease progression in heart failure with reduced ejection fraction (HFrEF) and are not addressed by neurohormonal antagonists (beta blockers, RAS inhibitors, and MRAs), which serve as the most commonly used evidence-based therapies in the contemporary management of HFrEF. By stimulating sGC and restoring the NO-cGMP pathway, vericiguat is a new treatment approach for patients with HFrEF who experience a worsening HF event despite treatment with guideline-directed medical therapy for HF.

2.1.4. Clinical presentation, diagnosis

HF is a clinical syndrome associated with a range of LV abnormalities and is categorized based on EF. HFrEF is commonly used to describe HF patients with an EF <40%, and heart failure with preserved ejection fraction (HFpEF) is used to describe HF patients with an EF ≥ 50% (Ponikowski et al. 2016). Patients with HF with EF in the 40-49% range have been underexplored in prior clinical studies and have no evidence-based HF treatment options. Registry data indicate that between approximately 40-60% of HF patients have HFrEF (Chioncel et al. 2017, Ibrahim et al. 2019). The broader vericiguat HF development program categorized patients with EF <45% as HFrEF and the remainder as HFpEF to investigate the full EF range of HF patients.

The clinical course for HFrEF patients is variable, with periods of stability punctuated by acute episodes of clinical decompensation with increased symptoms such as dyspnea, fatigue, and oedema. Even after successful recompensation, these events result in a worsening long-term prognosis as the risk for future decompensations increases, quality of life declines, and each recovery becomes less complete. This worsening of chronic HF has been defined in the "2017 European Medicines Agency Guideline on clinical investigation of medicinal products for the treatment of chronic HF (EMA 2017)".

Despite medical advances in the treatment of chronic HFrEF over the last 2 decades, patients continue to experience worsening HF events. Data from two retrospective studies analyzing insurance claims in the US reveal that up to 33% of HFrEF patients experience a worsening event (defined as HF hospitalization or IV diuretic use) within 12 months of the initial claim (Butler et al. 2020b, Mentz et al. 2020). Of the more than 5000 HFrEF patients enrolled in the European Society of Cardiology Heart Failure Long-term Registry, outcomes at 1 year indicated that 8.8% of patients had died, 31.9% were hospitalized for any reason, 14.6% were hospitalized for HF, and 21.2% were hospitalized for HF or died (Chioncel et al. 2017).

Worsening HF events are associated with a markedly poor prognosis as described in recent reviews of HF registry data. The ACC PINNACLE registry demonstrated that of the included 11064 HFrEF patients, 17% experienced a worsening HF event within 1.5 years following initial diagnosis, 56% of patients were rehospitalized within 30 days of the worsening event, and the 2-year mortality rate was 22.5% (Butler et al. 2019). A study examining data from a Medicare-linked Get-with-the-Guidelines-Heart-Failure registry found that 48.5% of HFrEF patients (defined as EF ≤40%) were readmitted within 5 years for HF, and 96.4% had a composite event of mortality/readmission within 5 years (Shah et al. 2017).

The high morbidity and mortality following a worsening HF event results in a significant burden to patients and leads to substantial healthcare resource utilization (Salem and ElKhateeb 2017).

2.1.5. Management

Current treatments for chronic HFrEF were established based on large randomized, controlled trials, with the results incorporated into guidelines issued by the ACCF/AHA and the European Society of Cardiology; these include Class I recommendations for beta-blockers, ACE inhibitors, ARBs, ARNIs, MRAs, and cardiac device therapies (McMurray et al. 2012, Ponikowski et al. 2016, Yancy et al. 2013b, Yancy et al. 2016a, Yancy et al. 2017). Additionally, the ACCF/AHA guidelines recommend combining hydralazine and isosorbide dinitrate for African Americans with NYHA Class III to IV receiving optimal therapy with ACE inhibitors and beta-blockers.

The guideline-directed use of HF therapies focuses on subsets of patients based on EF, renal function and potassium levels, and pre-existing ECG findings. Some patients, such as those with an EF >40% or eGFR < 30 mL/min/1.73 m2, do not meet the criteria for using certain guideline-recommended HF therapies. In addition, lack of tolerance to evidence-based medications may preclude the use or up-titration of the doses of these therapies. Therefore, due to differences in individual patient characteristics and tolerability, the application of guideline recommendations for each patient varies in clinical practice.

Although better adherence/compliance with existing drugs remains a medical goal, even patients on optimized therapy will continue to experience HF decompensation requiring additional therapies to provide long-term stabilization. Compared to the real-world experience, the use of evidence-based therapies to treat HFrEF is much better in large clinical trials. However, despite the use of evidence-based therapies in these studies, the rate of CV death and HF hospitalization remains unacceptably high in patients with HFrEF. Three recent trials illustrate the substantial residual risk despite optimal adherence to guideline-directed medical therapies in worsening chronic HFrEF patients (e.g., ASTRONAUT) as well as in those enrolling a more stable chronic HFrEF population (e.g., PARADIGM-HF and DAPA-HF).

In the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT), a placebo-controlled study evaluating hemodynamically stable patients recently hospitalized for HF (median 5 days after hospital admission) with a median NT-proBNP at randomization of 2718 pg/mL, there was a 17% 1-year CV

death rate and a 28% 1-year HF rehospitalization rate in the placebo group despite use of background guideline-directed medical therapy for HF (Gheorghiade et al. 2013).

Studies evaluating patients with more stable chronic HFrEF, such as PARADIGM-HF and DAPA HF, also demonstrate a substantial unmet medical need for patients treated with current guideline-directed medical therapy for HF. PARADIGM-HF was an active treatment controlled study in patients with stable chronic HFrEF who were randomized to either sacubitril/valsartan or enalapril in addition to guideline-directed medical therapies for HF following 2 sequential run-in periods of up to 8 weeks during the screening phase. In PARADIGM, the median NT-proBNP was 1608 pg/mL, and only 31% of the population had prior HF hospitalization within 6 months prior to screening (McMurray et al. 2014a, Solomon et al. 2016). The composite endpoint of CV death or HF hospitalization event rate was 21.8% (10.5 events per 100 patient-years), and the CV death rate was 13.3% (6.0 events per 100 patient-years) in the sacubitril/valsartan group over the 27-month median follow-up period (McMurray et al. 2014b, Srivastava et al. 2018).

DAPA-HF was a placebo-controlled study in patients with stable chronic HFrEF who were randomized to dapagliflozin or placebo, in addition to recommended therapy. In DAPA-HF, the median NT-proBNP was 1437 pg/mL, and only 16.4% of patients were hospitalized for HF within 6 months prior to study entry. The composite endpoint of CV death or HF hospitalization event rate was 16.1% (11.4 events per 100 patient-years), and the CV death rate was 9.6% (6.5 events per 100 patient-years) in the dapagliflozin group over the 18-month median follow-up period (McMurray et al. 2019a, McMurray et al. 2019b).

These recent trials illustrate the substantial residual risk for HF patients despite treatment with guideline-directed medical therapy for HF, including ARNI and dapagliflozin. These risks are particularly high for patients with worsening chronic HFrEF in whom the rate of the composite of CV death or HF hospitalization is higher than in patients with more stable chronic HFrEF (Gheorghiade et al. 2013, McMurray et al. 2014b, McMurray et al. 2019b, Srivastava et al. 2018). This morbidity and mortality in patients with worsening chronic HFrEF represent a significant unmet medical need, and the development of improved pharmacologic strategies for risk reduction is warranted (Ambrosy et al. 2014).

About the product

Mode of action

HF is associated with impaired synthesis of NO and decreased activity of its receptor, sGC. Soluble guanylate cyclase 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 sGC-derived cGMP contributes to myocardial and vascular dysfunction. Vericiguat restores the relative deficiency in this signalling pathway by directly stimulating sGC, independently of and synergistically with NO, to augment the levels of intracellular cGMP, a mechanism of action not currently addressed by the primary evidence-based therapies used in the contemporary management of HFrEF.

The agreed indication is:

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 (see section 5.1). The agreed posology is:

Vericiguat is administered in conjunction with other heart failure therapies.

Before starting vericiguat, care should be taken to optimise volume status and diuretic therapy to stabilise patients after the decompensation event, particularly in patients with very high NT-proBNP levels (see section 5.1). The recommended starting dose is 2.5 mg vericiguat once daily. The dose should be doubled approximately every 2 weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient.

If patients experience tolerability issues (symptomatic hypotension or systolic blood pressure [SBP] less than 90 mmHg), temporary down-titration or discontinuation of vericiguat is recommended (see section 4.4). Treatment should not be initiated in patients with SBP <100 mmHg (see section 4.4).

Type of Application and aspects on development

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a film-coated tablet containing 2.5 mg, 5 mg or 10 mg of vericiguat as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose, croscarmellose sodium, hypromellose 2910, lactose monohydrate, magnesium stearate and sodium laurilsulfate;

Film coat: iron oxide red (5 mg tablet only), iron oxide yellow (10 mg tablet only), hypromellose 2910, talc and titanium dioxide.

The product is available in transparent PVC/PVDC/Aluminium foil blisters and perforated unit dose blisters, transparent PP/Aluminium foil blisters and perforated unit dose blisters, and HDPE bottles with PP screw caps as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of vericiguat is methyl {4,6-diamino-2-[5-fluoro-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl}carbamate corresponding to the molecular formula $C_{19}H_{16}F_2N_8O_2$. It has a relative molecular mass of 426.39 g/mol and the following structure:

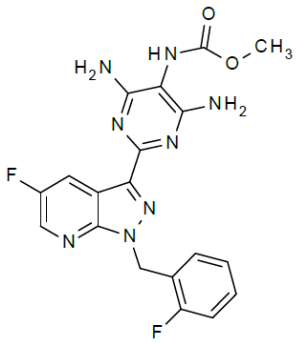


Figure 1: Active substance structure

The chemical structure of vericiguat was elucidated by a combination of IR spectroscopy, Raman spectroscopy, UV VIS spectroscopy, ^{1}H-NMR and ^{13}C-NMR spectroscopy, mass spectrometry and elementary analysis. The solid-state properties of the active substance were further investigated by x-ray powder diffraction, differential scanning calorimetry, thermogravimetric analysis and moisture sorption.

The active substance is a white to yellowish non-hygroscopic crystalline powder. It is practically insoluble between pH 3-7 and is very slightly soluble at more acidic pH. The active substance is micronized to improve solubility. Five polymorphic forms were identified during development, along with several solvated and hydrated forms and amorphous material. The chosen commercial polymorphic form (modification I) is routinely produced by the manufacturing process and is the most thermodynamically stable between -20 and 80°C. Vericiguat is achiral.

Manufacture, characterisation and process controls

Vericiguat is synthesized at one site in 3 main synthetic steps using well-defined starting materials with acceptable specifications and is subsequently micronized at a second site. The starting materials are considered acceptable, following submission of additional data on impurities in response to a major objection. This data had previously been stated to be necessary as part of a scientific advice procedure.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Proven acceptable ranges are defined for the stoichiometry of input materials for some steps and these have been adequately justified. No design space is claimed.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Fate and purge data were provided which demonstrates that the process as described provides active substance of suitable purity.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in a transparent LDPE foil bag which complies with the EC directive 2002/72/EC and EC 10/2011 as amended. The bag is stored within another tightly closed container for mechanical protection.

Specification

The active substance specification includes tests for appearance (material, colour), identity (IR, HPLC), particle size (laser diffraction), palladium (ICP-MS), water content (KF), residual solvents (GC), impurities (HPLC) and assay (HPLC).

The proposed limits are in line with ICH Q3A requirements. Limits for residual solvents and elemental impurities are set in line with ICH Q3C and Q3D respectively. Initially, the risk assessment for potential genotoxic impurities was lacking information and sufficient justification resulting in a major objection. In response, the applicant thoroughly discussed the potential presence of mutagenic impurities, including purge factor calculations and batch data. No controls on mutagenic impurities are required in the active substance specification as they are adequately purged by the manufacturing process. This is considered acceptable. The desired polymorphic form is routinely produced by the manufacturing process.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 3 production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 pilot to production scale batches of active substance from the proposed manufacturers stored in the intended commercial package for up to 12 months under long term conditions (25°C / 60% RH), for up to 12 months under intermediate term conditions (30°C / 75% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. Samples were tested for material and colour, polymorphic form, particle size upper X_{90}, water content, impurities and assay. All results complied with the proposed active substance specifications. There were no apparent trends observed.

Photostability testing following the ICH guideline Q1B was performed on 1 batch. In the solid state, vericiguat is photostable.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 24 months in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as film-coated tablets in three strengths as follows:

2.5 mg strength: Round, biconvex, white film-coated tablet with a diameter of 7 mm, marked with "2.5" on one side and "VC" on the other side.

5 mg strength: Round, biconvex, brown-red film-coated tablet with a diameter of 7 mm, marked with "5" on one side and "VC" on the other side.

10 mg strength: Round, biconvex, yellow-orange film-coated tablet with a diameter of 9 mm, marked with "10" on one side and "VC" on the other side.

The compositions of the tablets are qualitatively the same but quantitatively different: the 5 and 10 mg tablets are almost proportionate in terms of composition whereas the 2.5 and 5 mg tablets have the same overall weight. The tablets are distinguished by colour, markings and in the case of the 10 mg tablet, size.

The aim of the development was to provide an oral immediate-release formulation containing vericiguat as active substance to meet the posology and patient requirements.

The quality target product profile (QTPP) formed the basis of development. The critical quality attributes (CQAs) of the finished product were derived and defined as follows:

- Identity
- Appearance
- Assay
- Uniformity of Dosage units/Content uniformity
- Dissolution
- Degradation products
- Microbiological quality

Given the properties of the active substance, a wet granulation approach was adopted. The tablets are film-coated to facilitate swallowing and to add colour for tablet identification. Different excipients were investigated and the relative contents of the chosen excipients optimised. The excipients are typical of a tablet manufactured by wet granulation. All excipients are well known pharmaceutical ingredients and their quality or the quality of their constituents are compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

The QC dissolution method was shown to be sufficiently discriminatory.

Manufacturing process development is based on quality by design (QbD) principles including risk assessment using failure mode effects analysis (FMEA) methodology to identify relevant parameters to investigate experimentally. Investigations were conducted in both one factor at a time (OFAT) and multivariate (DoE) experiments to optimise process parameters. In this way, the process was optimized and a suitable control strategy established. No design spaces are claimed.

The primary packaging is transparent PVC/PVDC/Aluminium foil blisters and perforated unit dose blisters, transparent PP/Aluminium foil blisters and perforated unit dose blisters, and HDPE bottles with PP screw caps. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of seven main steps: mixing of intra-granular excipients, wet granulation with vericiguat, drying, sieving, blending with extra-granular excipients, compression and film-coating. The process is generally considered to be a standard manufacturing process. However, due to the low active substance content in the 2.5 mg tablet, that particular process is seen as non-standard.

Major steps of the manufacturing process have been validated on 3 production scale batches of each strength and the manufacturer plans to follow a continued process verification strategy during lifecycle.

This data was submitted in response to a major objection due to the non-standard process for the lowest strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls and overall control strategy are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release and shelf-life specifications for the 5 mg tablet include appropriate tests for this kind of dosage form including appearance (form, colour, markings), identity, uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), degradation products, assay and microbial purity (Ph. Eur.). The specifications for the 2.5 and 10 mg tablets are equivalent with the exception of their appearances.

A risk assessment on the potential formation of nitrosamine impurities was provided on request following a major objection since this was omitted from the initial submission. In conclusion, it can be considered that there is no risk of nitrosamines presence in the finished product and no specific control measures are needed.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Confirmatory batch analysis data from 2 batches of each strength in the 3 different packaging formats using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, it can be concluded that no additional controls for elemental impurities are required.

The proposed specification for the finished product is in line with ICH Q6A, and it is generally acceptable for this type of dosage form. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and degradation product testing has been presented.

Batch analysis results were provided for 3 pilot scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Compliant analysis data from batches used in phase III clinical trials was also provided.

The finished product is released on the market based on release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 batches of pilot scale batches of finished product stored for up to 24 months under long term conditions (25°C / 60% RH), for up to 24 months under intermediate conditions (30°C / 75% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. Supporting data were provided for batches stored refrigerated (up to 9 months) and frozen (up to 12 months). The batches are identical to those proposed for marketing and were packed in all 3 primary packaging formats (including 2 sizes of HDPE bottle) proposed for marketing. Samples were tested for appearance, degradation products, assay, dissolution and microbial purity. The analytical procedures used are stability indicating. No significant changes were observed under any of the tested conditions.

In addition, 3 batches of each strength were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Verquvo is considered to be photostable.

Samples were also exposed to high temperature (80°C) and high humidity (40°C / 75% RH in an open bottle). Despite the observed water uptake with high humidity and some within-specification degradation at high temperature, the samples were still very stable.

A temperature cycling study was also conducted which indicates that the finished product is stable to any short term temperature excursions during storage and transportation.

Based on available stability data, the proposed shelf-life of 36 months without specific storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

No other excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The major objections raised in relation to the choice of starting materials, risk assessment on genotoxic impurities, missing process validation data for a non-standard finished product manufacturing process and missing nitrosamines risk evaluation were all resolved by provision of additional data. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Nonclinical studies were performed to characterize the pharmacological properties of vericiguat *in vitro* and *in vivo*. The primary pharmacodynamics data for vericiguat include characterization of *in vitro* activity and mechanism of action, as well as *in vivo* assessments in functional assays and well-studied disease models. Furthermore, secondary pharmacodynamics data on off-targets from in vitro assays

are presented. The effects of vericiguat were investigated on vital organ systems (cardiovascular system including ECG, respiratory system and central nervous system) as well as on gastrointestinal function in several in vitro and in vivo safety pharmacology studies. Pharmacokinetic studies were conducted in rats and dogs. Interspecies comparison of metabolism, excretion, plasma protein binding and blood-to-plasma partition ratios was also performed. In addition, the potential of vericiguat as a substrate, inhibitor or inducer of various metabolizing enzymes and transporters was assessed. The toxicological program performed included studies to investigate the systemic toxicity as well as exaggerated pharmacological effects after repeated administration up to 26 weeks in rats and up to 39 weeks in dogs and in reproductive and developmental toxicity studies (including embryo-fetal development studies in rats and rabbits, fertility and early embryonic development and a pre- and postnatal development study in rats, and juvenile toxicity studies in rats), genotoxicity studies (bacterial mutagenicity and mouse lymphoma test in vitro and an evaluation of micronuclei in bone marrow of mice and in peripheral blood of rats in vivo) and 2-year carcinogenicity studies in rats and mice as well as studies addressing specific questions (phototoxicity, toxicity profile in pigmented rats).

2.3.2. Pharmacology

Primary pharmacodynamic studies

The nitric oxide (NO), soluble guanylyl cyclase (sGC) signalling pathway is one of the key regulators of the cardiovascular system. The sGC is ubiquitously expressed and serves as the receptor for the endothelium-cell-derived NO. Upon NO binding, sGC catalyzes the generation of the signalling molecule cyclic guanosine monophosphate (cGMP) that plays a pivotal role in regulating cellular functions, such as vascular tone, proliferation, fibrosis and inflammation (Stasch and Hobbs 2009, Stasch, Pacher et al. 2011, Sandner, Zimmer et al. 2018).

The pathophysiology of cardiovascular diseases and heart failure includes endothelial cell dysfunction, which impairs NO production leading to decreased NO availability and reduced cGMP tissue levels. This reduced NO availability and insufficient stimulation of sGC result in systemic, coronary, pulmonary, and renal vasotone dysregulation, organ damage and dysfunction driven by perfusion disturbances, adverse remodelling, and manifestation of the cardio-renal syndrome.

In vitro:

Vericiguat (also referred to as BAY 1021189 or MK-1242) is an sGC stimulator. Vericiguat selectively and specifically binds to the sGC leading to concentration-dependent cGMP production. When tested in a cell-free system using purified sGC, vericiguat was able to stimulate cGMP production in a concentration-dependent manner. cGMP production was stimulated from 1.7 fold to 57.6 fold relative to no stimulation after exposure to Vericiguat from 0.01 µM to 100 µM. The NO donor diethylamine/NO complex (DEA/NO) appears to have a synergistic effect on cGMP production by sGC, when combined with Vericiguat. The stimulatory effect of vericiguat on sGC can be inhibited by sGC inhibitor 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ). In a luminometric guanosine triphosphate (GTP) consumption assay, the minimal effective concentration (MEC) of vericiguat for the soluble guanylate cyclase enzyme activity in the presence of NO donor, linsidomine (SIN 1), appears to be 120 nM. The MEC is the concentration where the enzyme's velocity is increased by a factor of 2 compared to basal enzyme activity.

Vericiguat was further tested in cell systems. Rat sGC overexpressed by recombinant CHO cell line was concentration-dependently stimulated by vericiguat with an EC50 value of 1005 ± 145 nM, which could be even more stimulated by the addition of NO donor S nitroso-N-acetyl-D,L-penicillamine (SNAP) also concentration-dependently. The M-1 metabolite (BAY 1222707) was not pharmacologically active when

tested up to 10 µM in this same assay. Overexpression of the particulate GC isoforms GC-A and GC-B in CHO cells showed no activity when exposed to vericiguat, thus indicating high specificity for sGC. Similar results on sGC stimulation, blockade and synergism were seen in porcine endothelial cells,

Several ex vivo studies were performed to further investigate the effects of vericiguat. Vasorelaxant properties of vericiguat were investigated on rings of rabbit saphenous artery, rabbit aorta, canine femoral vein and porcine coronary artery. Induced contractions were inhibited by vericiguat with IC50 values of 798 nM, 692 nM, 3,072 nM and 956 nM, respectively. As chronic administration of organic nitrates invariably leads to the rapid development of tolerance, the IC50 of vericiguat for inhibition of induced contraction of isolated saphenous artery rings taken from normal and nitrate-tolerant rabbits was analysed. Vericiguat acts similar on both normal (IC50 of 5.6 nM) and nitrate tolerant (IC50 of 5.8 nM) saphenous artery rings of rabbits, indicating that nitrate tolerance is not a limiting effect on vericiguat activity. These latter IC50 values (Study 36443), however, are >100-fold lower than the previous reported IC50 value (Study 36442) for rabbit saphenous artery rings of 798 nM. Apparently, also the IC50 of the control NO-donor glycerol-trinitrate (GTN) varied (> 1000 fold) between the two studies. It is considered that such a variation between studies using the same tissue model is quite large. The results of these studies should thus be interpreted qualitatively and not quantitively. In an ex vivo experiment in Langendorff perfused isolated rat heart, vericiguat reduced dose-dependently the perfusion pressure of isolated rat hearts with significant effects at 1 and 10 µmol/l. Parameters such as heart rate, left ventricular diastolic pressure (LVDP), and +dP/dtmax, were not changed by the application of the compound up to the concentration of 10 µmol/l. However, heart rate, left ventricular pressure and contractility were effected in in vivo models described below.

In vivo:

in vivo pharmacodynamic studies were conducted in healthy rats and dogs, spontaneous hypertensive rats (SHR), a hypertension and heart failure model (renin-transgenic rats), a dog and minipig model of pulmonary arterial hypertension (PAH), and a dog model of pulmonary hypertension secondary to left ventricular dysfunction (PH-LVD).

Rats: In healthy rats, single oral or IV dosing of up to 10 mg/kg resulted in a dose-dependent decrease in arterial blood pressure was observed, with a compensatory increase in heart rate, which was most prominent in animals dosed with the highest dose. Effects normalized to control levels at 20 hours after administration. In spontaneously hypertensive rats, a single dose of up to 3 mg/kg, or repeated dosing for 12 days up to 10 mg/kg, caused a decrease in mean arterial blood pressure lasting for 24 hours or more. This was only evident from doses of 3 mg/kg or higher. A compensatory tachycardia effect was seen in the first 12 hours after dosing, but was transient and lasted for only a few days. In a hypertension and heart failure model (Renin- transgenic rats), besides the reduction in arterial blood pressure, survival was increased by 70% and 90%, for rats treated with 3 mg/kg or 10 mg/kg vericiguat, compared to only 25% in the placebo-treated rats. In addition, a wide variety of plasma and urine markers, as well as gene expression profiles of heart and kidneys, indicated a functional improvement of heart and kidney function and protection of the heart and the kidneys in these rats.

Dogs: Healthy anaesthetized dogs were dosed up to 300 µg/kg vericiguat. Reductions in mean aortic blood pressure (mAoP) were accompanied by a decrease in systolic left ventricular pressure (sLVP), left ventricular end-diastolic pressure (LVEDP), central venous pressure (CVP), and systemic vascular resistance (SVR) and a moderate reflex increase in heart rate (HR) and left ventricular contractility (+dP/dt). In addition, the higher dose of 300 µg/kg showed a long-lasting decrease in pulmonary artery pressure (PAP). A positive shift in the myocardial oxygen balance was also indicated. The cardiovascular effects lasted for several minutes only. These effects were also seen in a dog model of PAH, which also showed effects on vascular relaxation and resistance. In the PAH model, the cardiovascular effects lasted for the complete 50 min observation period. Higher doses of up to 3

mg/kg were used in a dog model of PH-LVD. This model showed a preferential vasodilation in the pulmonary vascular bed, as opposed to the systemic circulation. However, this experiment is hampered due to limited data points.

Minipigs: In a minipig model of PAH, doses of up to 300 µg/kg vericiguat resulted in a dose-dependent decrease of pulmonary as well as systemic artery pressure. As with the PH-LVD dog model, effects on pulmonary pressure were slightly more pronounced.

Taken together, the pharmacodynamic effect seen in the in vivo studies with vericiguat is consistent with its mechanism of action, i.e. stimulation of the NO-sGC-cGMP pathway, leading to vasodilatation.

Secondary pharmacodynamic studies

The specificity of vericiguat was tested to a broad range (n=110) of off-targets by means of radioligand binding and enzyme assays. At a concentration of 10 µM, no interference with any of these off-targets was detected except for an inhibition of the human dopamine transporter (IC50 of 2.9 µM). Moreover, vericiguat showed no meaningful anti-aggregation effects on adenosine diphosphate (ADP), thrombin receptor activator peptide 6 (TRAP-6), and collagen-induced human platelet aggregation in vitro. Furthermore, the human major circulating metabolite M-1 was investigated in radioligand binding and enzyme assays without any interference to the 77 off-targets tested at 10 µM.

In summary, vericiguat and its metabolite M-1 does not exhibit meaningful off-target pharmacological activity or effects on platelet aggregation in vitro at concentrations up to 162 fold the effective human free plasma exposure of vericiguat at a steady state (Cmax,u,ss 17.9 nM).

The absence of in vivo studies to assess secondary pharmacology is agreed.

Safety pharmacology programme

Central nervous system

Several studies in rats were performed to investigate the effect of vericiguat on the central nervous system. Parameters studies were behaviour, locomotion, body temperature regulation, motor coordination, and chemo-convulsion. No effects were observed at doses, which resulted in exposures well above the clinical exposure based on Cmax and AUC.

Respiratory system

No effect on the respiratory system was observed in rats dosed with vericiguat, which resulted in exposures well above the clinical exposure based on Cmax and AUC.

Gastro-intestinal system

The effect of vericiguat on gastric emptying and small intestinal transit of $BaSO_4$ was assessed in rats. Vericiguat most probably due to its mode of action as an sGC stimulator, having a relaxing effect on smooth muscle cells, inhibited intestinal transit at doses of $\geq$ 5 mg/kg in male rats, which compares to an unbound Cmax of 16.1 µg/L and an unbound $AUC_{0\text{-}24}$ of 150.3 µg·h/L are only slightly above the clinical Cmax of 7.6 (µg/L) and the clinical $AUC_{0\text{-}24}$ of 145.6 (µg·h/L). Gastric emptying was unaffected at all dose groups. Effects on intestinal transit can therefore not be excluded. In the clinical trials adverse effects on the gastrointestinal tract have been seen, and this is sufficiently covered in the SPC and RMP.

Cardiovascular system

The potential of Vericiguat to have intrinsic effects on the hERG K+ current was assessed *in vitro* in stably hERG-transfected HEK293 cells by means of the whole-cell voltage-clamp technique at a concentration range in accordance to ICH S7B guideline. Vericiguat reached a threshold (IC_{20}) and half-maximal inhibitory concentrations (IC_{50}) for hERG channel inhibition at approximately 1.9 µM and 9.9 µM, respectively. The clinical unbound Cmax is 7.6 µg/L that equals to a molar concentration of 17.8 nM ~0.02 µM, which is well below the clinical molar concentration.

In vivo in dogs and rats, vericiguat caused a dose-dependent decrease in arterial blood pressure, particularly in systolic blood pressure (up to 23%) starting already at the low dose of 0.6 mg/kg, which was not fully reversible within the 16 hours observation period. However, this can be regarded as a pharmacologic effect. Probably as a counter-regulation to the vasodilation, the heart rate was increased (up to 68%). Along with the increased heart rate, the PQ and QT intervals were shortened. When corrected for heart rate, the QTc intervals were not prolonged. No drug-related effects on body temperature were observed. Thus apart from the pharmacologic-related effects, no influence on cardiac parameters was found up to a dose of 6 mg/kg, which relates to plasma concentrations well above the clinical exposure based on Cmax and AUC.

Pharmacodynamic drug interactions

No pharmacodynamic interactions, e.g. over-additive effects of vericiguat were noted when co-administered orally with GTN on heart rate, blood pressure and ECG in rat and dogs, nor on top of a double combination of the NEP inhibitor AHU377 and ARB valsartan on circadian blood pressure and heart rate in rats.

2.3.3. Pharmacokinetics

Pharmacokinetic (PK) studies were conducted in rats and dogs, the primary safety assessment species. Interspecies comparison of metabolism, excretion, plasma protein binding and blood-to-plasma partition ratios was also performed. Toxicokinetic profiles following repeated dosing were characterized in mouse, rat and dog following oral dosing for a total duration of up to 39 weeks and in the carcinogenicity studies in rat and mice (104 weeks). In addition, exposure was characterized as part of the Embryo-Fetal Development Studies in rats and rabbits.

Methods of analysis

^{14}C-Vericiguat (labelled in the pyrimidine moiety) was used for the determination of radioactivity concentration in body fluids, organs and tissues and in excreta (by liquid scintillation counting) and for QWBA (by radioluminography).

Plasma concentrations of Vericiguat and the M-1 metabolite were determined by high-pressure liquid chromatography (HPLC) - tandem mass spectrometry (MS/MS) methods following protein precipitation. The provided validation reports demonstrate that the assays were sensitive, selective, and suitable for assessing Vericiguat concentrations in mouse, rat, rabbit, and dog plasma or M-1 concentrations in mouse and rat plasma. The lower and upper limits of quantitation (LLOQ and ULOQ) were 1-5 µg/L and 1000 µg/L, respectively for the Vericiguat assays and 2-5 µg/L and 1000 µg/L, respectively for the M-1 assays.

Absorption

A single dose pharmacokinetic study following IV or oral administration of vericiguat was performed in male rats and female dogs. Vericiguat exposure increased dose-proportionally at 0.03-0.6 mg/kg in dogs and 0.3-3 mg/kg in rats, but more than dose-proportional in rats at 3-10 mg/kg. Tmax ranged

from 1-3h in rat and 0.5-1.8h in the dog. The steady-state volume of distribution is low (0.8-1.1 L/kg). Terminal elimination half-life (T1/2) was between 2.45-3.31h in rat and 4.9-6.9h in dogs. Plasma clearance was low (0.15 – 0.21 L/h/kg). The oral bioavailability of vericiguat was 39-47% in rat and 72-75% in the dog.

Multiple-dose toxicokinetic studies were performed in mice (administration via diet), rats and dogs (gavage). In general, exposure increased dose-proportionally. Minimal accumulation was observed following repeated dosing in rats (R = 1.1-1.9), but not in dogs (R = 0.8-1.5). In mice, exposure in males was slightly higher than in females (<2), but in rats and dogs, exposure in females was slightly higher than in males. In dogs, dose normalised exposure in the 2 and 4-week studies was much lower than in the single-dose, 13 week and 39-week studies (604-2613 µg·h/L in the 2-week study, 1173-2556 µg·h/L in the 4-week study versus 3250-6567 µg·h/L, 4240-4656 µg·h/L and 2400-4800 µg·h/L in the SD, 13 and 39-week studies, respectively). This is probably because in the 2-week study, a tylose suspension was used instead of the EtOH 10%, PEG400 60%, water 30% or PEG400 solution used in the other studies. In addition, in the 4 week study, a different strain of Beagle dogs was used, as well as higher dose levels.

In pregnant rats, exposure was similar as in non-pregnant rats and exposure increased in a dose-proportional manner. In pregnant rabbits, however, the increase in exposure was supraproportional.

In the carcinogenicity studies in mouse and rat, the toxicokinetics of the metabolite M-1 were also assessed. Exposure of M-1 increased in a dose-proportional manner in both species. In the rat (but not in mice) some accumulation occurred following repeated dosing (R=2.7-3.6 at day 359). It is noted that in the toxicokinetic study (a part of carcinogenicity study) in rats with M-1 showed that there was a large variation in Cmax values in female and male rats at 359 days, and the results are presented as pooled results (R-13305). However, this was not done in M-1 toxicokinetic studies in mice (R-13312).

Distribution

The extent of plasma protein binding of vericiguat was evaluated in plasma from mouse, rat, rabbit, dog, monkey and human using ultracentrifugation. Plasma binding was species-dependent, with unbound fractions of 2.2 in human, 3.7 in rabbit, 4.6 in rat, 5.6 in monkey, 8.0% in mouse and 10.2% in the dog. Vericiguat was mainly bound to serum albumin. Unbound fractions of the metabolite M1 ranged from 1.6% in humans to 15% in rat and dog. Blood: plasma ratio was 0.79 in rat, 0.87 in dog and 0.66 in human.

Tissue distribution of vericiguat was investigated in albino (Wistar) and pigmented (Long Evans) rats using quantitative whole-body autoradiography (QWBA) following a single oral administration of 3 mg/kg [14C]vericiguat. Vericiguat was widely distributed. At 24h post-dose, exposure in organs, tissues and blood was 4 times higher in females than in males. The highest concentrations were observed between 2 and 4 hours post-dose in kidney cortex and outer medulla, adrenal cortex (tissue-blood ratios 5-6) and liver, Harderian gland, and kidney inner medulla (tissue blood ratio 2-3). The lowest concentrations were found in the brain and bone. Elimination from tissues was rapid, with half-lives of 1.5-3 h.

In pigmented rats, high exposure was observed in the pigmented eyewall, highly pigmented skin areas, and adrenals (tissue: blood ratios >100, 8 and 5, respectively); however, there was no evidence for phototoxicity. Melanin binding of vericiguat and/or its metabolites was also observed for the substantia nigra. Elimination occurred with longer terminal half-lives in melanin-containing tissues (161 and 344h for pigmented eyewall and highly pigmented skin, respectively.

Placental transfer of vericiguat was assessed by QWBA in pregnant rats following a single oral dose of 3 mg/kg on gestational day 19. The distribution pattern of radioactivity in dams was similar to that in non-pregnant rats. Based on AUC(0-48), the fetal blood radioactivity exposure was 67% of the

maternal blood exposure. The exposure ratio's for fetal skeletal muscle/maternal skeletal muscle and fetal brain/maternal brain were 0.9 and 5.8, respectively.

Following a single oral dose of 1 mg/kg to lactating rats on lactational day 8, vericiguat-related material was shown to be secreted into milk. Approximately 12% of the dose was excreted in milk at the 2 sample intervals (8 and 24h).

Metabolism

In the presence of liver microsomes from mouse, rat, rabbit, dog, monkey and human, only low turnover was observed. Isomerization of the methylcarbamate moiety to an adjacent amino group leading to M-9 was the main pathway. When incubated with fresh rat, dog, and human hepatocyte suspensions, low turnover was observed. N-glucuronidation of vericiguat (formation of M-1) was the major biotransformation pathway in all species investigated.

The *in vivo* metabolism of vericiguat was investigated in mouse, rat, dog and human. Following oral administration, vericiguat was the main component (>95%) in plasma of mouse, rat and dog. Metabolite M-1 (the N-glucuronide of vericiguat) was a minor component (1.5, 1.6 and 1.6%, respectively). In humans, however, M-1 was a major metabolite (see clinical part).

Excretion

Excretion of [^{14}C]vericiguat was investigated in male rats (intact and bile duct cannulated) following oral (3 mg/kg) or IV (1 mg/kg) administration. Vericiguat was rapidly excreted (>85% within 24h). In intact rats, faeces was the primary route of excretion (81%), while 11% was excreted via urine (following oral administration). A study in bile duct cannulated rats showed that biliary excretion accounted for 35 (oral) to 43 (IV)% of the administered dose. Following IV administration, 2.6% of the dose was recovered in the gastrointestinal tract and 30% in faeces, indicating intestinal secretion. Vericiguat was mainly excreted as a parent compound (70 and 9% of the dose in faeces and urine, respectively). The main metabolites in feces were M1 and the hydroxylated metabolites M-3, M-4, and M-5 (9.5% of the dose) and in urine M-1, M-2, M-3 and M15 (each <1% of the dose).

Also in dog vericiguat was mainly excreted via faeces (89.2%; 4.4% via urine) following a single oral dose (0.6 mg/kg). In urine, the majority was excreted as parent compound (2.35% of the dose), together with several minor metabolites, whereas in feces 51% was excreted as M-1, 19% as vericiguat and 8% as the hydroxylated metabolite M-3.

In contrast, human excretion via urine played a much larger role: 53% was excreted via urine and 45% via faeces. In urine, the majority was excreted as metabolite M-1 (41%). Nine % was excreted as the parent compound and 2% as metabolite M-15. In faeces, 43% was excreted as the parent compound and 1.6% as M-15, whereas M-1 was not detected, possibly due to hydrolytic cleavage into vericiguat by microbial flora.

Pharmacokinetic drug interactions

The results of the studies on the pharmacokinetic drug interaction potential will be evaluated in the clinical assessment report.

2.3.4. Toxicology

Single dose toxicity

No single dose toxicity studies were performed.

Repeat dose toxicity

Repeated dose toxicity studies were conducted up to 13 weeks in mice, up to 6 months in rats, and 39 weeks in dogs.

Many of the observed effects observed in the repeated dose studies can be considered to be due to the pharmacological action of vericiguat. Decreased blood pressure in dogs and vasodilation, visible as prominent vessels in the heart in rats and myocardial arteries hypertrophy in dogs, occurred due to smooth muscle cell relaxation. Adrenal gland hypertrophy, primarily in zona glomerulosa and fasciculata is a sign of activation of the renin-angiotensin-aldosterone system. Decreased creatinine (mice), decreased cholesterol and triglycerides (rats) and decreased thrombocytes (rat) may be due to hemodilution as a result of vasodilation. Water consumption was increased in mice and rats, and urinary volume was increased. Gastrointestinal effects were observed, such as dilated cecum in mice, diarrhoea and prominent Paneth cells in rats and vomiting, salivation and, a more serious effect, rectal prolapses in dogs. Gastrointestinal effects are attributed to the pharmacological action of vericiguat via smooth muscle relaxation.

A serious effect on bone (remodelling/hyperostosis and thickened growth plate) was observed in rats, but not in mice or dogs. It was observed in the 2-week, 4-week and 13-week studies but not in the 6-month study nor in the carcinogenicity study in rats. In the 4-week study, this effect was reversible in females but only marginally reversible in males after 2 weeks of recovery.

In all the repeat-dose toxicity studies in rats, crystal-like structures were observed in the urinary sediment. The crystals observed at ≥15 mg/kg (4-week study) or ≥10 mg/kg (13-week and 26-week study), i.e. at exposure levels corresponding to 7-fold the human therapeutic exposure (total AUC) or 14-fold (unbound AUC) and above. The crystal-like structures were not associated with any degenerative, regenerative, inflammatory or hyperplastic findings in the upper and lower urinary tract in any study. After chronic treatment up to >20-fold (based on total AUC) or approx. 50-fold (based on unbound AUC) the human therapeutic exposure, the crystals were not associated with adverse effects.

Effects on the reproductive organs were observed at high doses in mice and rats. In mice, decreased corpora lutea were observed in the ovaries (safety margin for this effect 42 based on unbound AUC0-24h). In rats, prostate / seminal vesicles atrophy (safety margin 48) and uterus atrophy (safety margin 31) were observed. In dogs, prostate acinar atrophy was observed at lower dose (5 mg/kg/day).

Genotoxicity

Vericiguat was not genotoxic in an Ames test, a mouse lymphoma assay, and *in vivo* micronucleus assays in mice and rats.

Carcinogenicity

In mice, numbers of tumours were not increased up to 150 mg/kg/day in males and 250 mg/kg/day in females (exposure multiple based on unbound AUC 149 and 286 in males and females respectively). Ovary tubulostromal, cystopapillary and luteal cell hyperplasia, which were observed in female mice at doses ≥ 50 mg/kg/day, are expected to be age-related, considering that these are age-related effects and that survival was low in the control group in female mice compared to the treated groups.

In male rats, pheochromocytoma and Leydig cell adenoma were observed. A (small) increase in pheochromocytoma was observed at doses ≥ 6 mg/kg/day, with exposure multiple in males based on

unbound AUC (1403 µg.h/L) of 9.6. An increase in Leydig cell adenoma was observed at 20 mg/kg/day, with exposure multiple based on unbound AUC (5382 µg.h/L) of 37.

Reproduction Toxicity

No effect on fertility was observed in rats up to 50 mg/kg/day. No toxicokinetics were performed in the fertility study but based on the embryo-foetal development study in rats, the exposure multiple of vericiguat based on unbound AUC at 50 mg/kg/day was approximately 75.

In an embryofoetal development study in rats, the only abnormal finding in the offspring was thymus extended cranially, which is of uncertain relevance. This was, however, only seen at the highest dose of 50 mg/kg/day (exposure multiple of vericiguat 75 based on unbound AUC0-24h) and therefore considered not clinically relevant. In rabbits, abortions were observed at 2.5 mg/kg/day (exposure multiple of vericiguat based on unbound AUC0-24h 6). At the NOAEL of 0.75 mg/kg/day, exposure was similar to clinical exposure. Although it was not shown to be caused by the pharmacodynamic effects of vericiguat, this is very well possible, for instance, if blood pressure was decreased (not measured in rabbits).

In a pre-and postnatal development study in rats, an increased incidence of stillbirths and decreased pup survival of the F1 generation was observed at 30 mg/kg/day. A delay in incisor eruption and vaginal opening and decreased pup body weight gain was observed at 7.5 mg/kg/day. A delay in balano-preputial separation was observed at 30 mg/kg/day. No effect on the F2 generation was observed. No toxicokinetics were performed in the peri- and postnatal development studies. At 30 mg/kg/day, the exposure multiple for vericiguat based on unbound AUC in the 26-week rat study was 52. Pup mortality was not increased at 15 mg/kg/day at an exposure of approximately 21x the human exposure (based on unbound AUC from the embryofoetal development study).

In adolescent rapidly-growing rats, effects on bone were observed as described above. The NOAEL for this effect was in general 10-15 mg/kg/day (and 30 mg/kg/day in females in the 2-week study), with safety margins based on unbound AUC0-24h in the repeated dose studies of 10-31 and in the juvenile toxicity studies of 3-10. In juvenile rats, necrotizing enteritis was observed at 10 mg/kg in the pivotal juvenile toxicity study (13-week group). This occurred within the first 2 weeks of the study. It seems likely that this was an incidental outbreak, which may have been caused by anaerobic bacteria for which the inhibited gastrointestinal tract mobility may have increased the predisposition. It was not observed in the rats in the 4-week group in the pivotal juvenile toxicity study, nor in the 4-week pilot juvenile toxicity study, with doses up to 30 mg/kg. Also, in the juvenile rat study, at the highest dose of 10 mg/kg/day, 15 rats died during the first 2 weeks of treatment likely due to gavage errors but in 5 of these, the cause of death could not be determined in these decedents due to cannibalism after death and in 2 due to autolysis. According to the study report, this is a common phenomenon in juvenile studies. It is, however, remarkable that all these cases occurred in the high dose group. It is not clear if there could be a vericiguat-related component indicating an effect on behaviour in this phenomenon.

Local Tolerance

Effects observed on the gastrointestinal tract, as described above, were most likely due to the pharmacological action of vericiguat and not due to local toxicity.

Other toxicity studies

Antigenicity and immunotoxicity

There were no observations or changes considered to be due to potential antigenicity induced by vericiguat in the routine repeat-dose toxicity studies. Therefore, no antigenicity/immunogenicity evaluations were conducted.

Apart from an occasional decrease in leukocytes and lymphocytes in rats at the highest tested dose only (100 mg/kg/day), no effects were found on the immune system in the repeated dose studies. It is therefore agreed that no immunotoxicity studies were performed.

Dependence

Vericiguat does not bind to neurotransmitter receptors or transporters at clinically relevant concentrations. Quantitative whole-body autoradiography in rats indicates that vericiguat does not readily cross the blood-brain barrier. Additionally, as a P-gp substrate, vericiguat will be actively transported out of the brain. There was no evidence of direct CNS activity in safety pharmacology or in routine repeat-dose toxicity studies. Behavioural findings (including minor gait/posture abnormalities, hypoactivity, and minor delay of the righting reflex) observed sporadically in rats at high exposures were not a direct CNS effect but were considered secondary to vascular smooth muscle cell relaxation, vasodilation and decreased blood pressure/body temperature. Importantly, such a pharmacologic profile is not consistent with drug abuse liability risk. Therefore, due to the low potential for CNS exposure, the absence of CNS-related findings in safety pharmacology and in repeat-dose toxicity studies in rats and dogs, nonclinical abuse liability studies were not performed with vericiguat.

Metabolites

M-1 is a major metabolite in humans. Although it was only a minor component in plasma of non-clinical species, the exposure to M-1 in the toxicology studies was sufficient. Also, M-1 is not pharmacologically active up to a concentration of 10 µM and shows no relevant off-target activity in radioligand assays on binding to 77 targets (receptors, transporters and enzymes) tested at 10 µM. It is therefore agreed that no additional studies with M-1 were performed.

Studies on impurities

There are no impurities specified at levels above the qualification limit according to Guideline ICH Q3A. There are however many potential impurities which had to be checked for genotoxic alerts.

A total of 24 potential impurities were negative for genotoxic alerts in both DEREK and Leadscope. Nine impurities with a structural alert for genotoxicity in silico, tested non-genotoxic in the Ames test. Two additional impurities had the same structural alert and similar structure as two of the impurities with a negative Ames test and were therefore also considered non-genotoxic. Nine impurities had a structural alert in Leadscope based on the pyrazole structure. The pyrazole moiety is also present in vericiguat, which was negative in the Ames test. These potential impurities are therefore considered non-genotoxic.

Pteridinetriamine had an alert in Leadscope based on the aromatic amines moiety. It was considered non-genotoxic because a negative Ames test was available for an intermediate (BAY 3463663). Because the structure of this intermediate contains the group causing the alert, and the structure of this intermediate is part of the structure of pteridinetriamine, the latter can be considered non-genotoxic as well.

Fluoroazopyrimidine and 2-phenyl-fluoroazo_pyrimidine contain an alert for an azo group. They are nearly identical or very similar to BAY 576290, for which a negative Ames test is available. These compounds can be considered sufficiently related to BAY 576290 to conclude that they are non-genotoxic based on this Ames test.

Fluoroazopropene_nitrile and iminomethyl_pyrazolopyridine are considered non-genotoxic by the Applicant because they share an alert for mutagenicity based on the aromatic azo moiety (330 Aromatic azo compound), which is also present in the structurally similar compound BAY 576290, which was negative in the Ames test. A follow-up Ames test was performed for these impurities, which were negative for mutagenic potential.

Bispyrazolopurinamine and fluoropurinamine are considered non-genotoxic by the Applicant because they share the aromatic amine moiety with the compound CAS 2922-28-3 negative in the Ames test. However, apart from the polycycle aromatic amine moiety, the structures of bispyrazolopurinamine and fluoropurinamine are very different from CAS 2922-28-3. Therefore, no conclusion can be drawn regarding the non-genotoxicity of bispyrazolopurinamine and fluoropurinamine, based on the Ames test for CAS 2922-28-3. Ames tests were performed with bispyrazolopurinamine and fluoropurinamine, and were found to be negative for mutagenic potential.

The following potential impurities are considered genotoxic and/or carcinogenic and are controlled at levels below 30% of the TTC, i.e. below 0.5 µg/day for each of these impurities: aminopyrazole, chlorobutylmethylcarbamate, 4-chloro-1-butanol, hydrazine and methyl methanesulfonate. For aniline, a lifetime PDE of 720 µg/day is established (ICH M7). The estimated maximal intake of aniline is 0.51 µg/day (51 ppm) at the maximally recommended dose of 10 mg/day.

Dimethylimido_formamide is considered non-genotoxic because it shares an aromatic imine moiety with chlorphenamidine. The structures of dimethylimido_formamide and chlorphenamidine are, however, not very similar. However, after a change of solvent during the manufacturing process, dimethylimido_formamide is no longer expected to be present in the final product. Chloromethyltriethylammonium_salt and TF-propyltosylate are considered genotoxic but are not expected to be present in the final product.

Phototoxicity

Vericiguat was not phototoxic in an *in vitro* 3T3 NRU phototoxicity assay.

2.3.5. Ecotoxicity/environmental risk assessment

Vericiguat is not PBT, nor vPvB. The PECsw is 0.05 µg/L, which exceeds the action limit of 0.01 µg/L. Therefore, a Phase II assessment was performed. Vericiguat is persistent in the water:sediment simulation study. The substance meets the vP criterion. This has, however, no consequences since the substance does not meet the B and T criteria. A risk assessment for the terrestrial compartment is not triggered, since Koc sludge values are <10,000 L/kg. A risk to the STP, surface water, groundwater and sediment compartment is not anticipated based on the prescribed use of vericiguat.

Considering the provided data, vericiguat is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Pharmacodynamics

The mode of action and proof of concept of vericiguat was adequately investigated by the applicant. Vericiguat binds specifically and with a high affinity to sGC. Overall, in vivo proof of concept has been demonstrated using healthy animals and several animal models. There is no secondary binding of vericiguat on any other receptor of the enzyme, and no effects on the major organ systems in safety pharmacology studies, except for the anticipated decreased blood pressure and increase in heart rate.

It is noted that the pharmacology and toxicology of vericiguat is very similar to that of riociguat, which has been approved for the treatment of pulmonary hypertension. The Applicant has performed only two studies in animal heart failure models (a low-NO rat model of hypertension and heart failure, dogs with heart failure induced by tachypacing). Therefore, from a pharmacological point of view, there is only weak evidence for therapeutic efficiency in the claimed indication (treatment of HFrEF). The applicant explained that the choice for the indication was not solely based on the two relevant preclinical studies presented amongst others in the development program. Also, preclinical information and clinical information with other sGC stimulators present in the public domain was considered as support for the intended pharmacological effect of vericiguat in the proposed indication. Another argument for clinical investigation of the potential of vericiguat in HFrEF patients was also based on the high clinical need for treatment in this indication. This approach can be followed and it is agreed that the support for the indication of the treatment is mainly based on the outcome of the clinical studies (VICTORIA trial).

The EC50 values for stimulation of sGC by vericiguat are in the concentration range of 10 – 1000 nM, whereas the therapeutically effective free plasma concentration is only about 17 nM. It is not clear whether this indicates that at therapeutically effective free plasma concentrations of vericiguat, only sub-maximal stimulatory effects on sGC occur. The applicant noted in this respect that in the in vitro assays, a clinically present effector (endogenously produced NO) is not present. This factor is not easily modelled in in vitro assays as the endogenous NO production is very difficult to quantify and could vary significantly, depending, e.g. on disease and comorbidities. It is agreed with the applicant that the clinical effective and safe concentration is determined based on the clinical efficacy and safety data.

Pharmacokinetics

From the pharmacokinetic point of view, mouse, rat and dog were the most relevant species for non-clinical efficacy and safety studies. After repeated exposure, systemic exposure of vericiguat increased in an approximately dose-proportional manner.

Toxicology

In the repeated dose toxicity studies, effects were observed which can be considered to be due to the pharmacological action of vericiguat and which were generally not serious at clinical exposures. A more serious effect was rectal prolapses in dogs. Rectal prolapses in dogs occurred only at doses $\geq$ 7.5 mg/kg/day (4-week study), but not at 5 mg/kg/day in the 13-week and 39-week studies. Safety margins ranged 4-15 for this effect in dogs.

Vericiguat was shown to be non-genotoxic, and it did not induce tumours in mice. In male rats, a small increase in pheochromocytoma and Leydig cell adenoma was observed. Rats, in particular male rats, are known to be much more sensitive to the development of pheochromocytomas than humans. Though there appears to be a dose-response relationship in pheochromocytomas in male rats, the increase was not statistically significant. No increase in pheochromocytomas was observed in female rats and in mice. Overall, the pheochromocytomas are considered not relevant for humans. The Leydig cell adenoma is reported to be caused by prolonged activation of the renin-angiotensin-aldosterone system (due to prolonged decreases in blood pressure), leading to the secretion of catecholamines and consequently resulting in the stimulation of Leydig cells due to the triggering of luteinizing hormone (LH). This mechanism is plausible. The decrease in blood pressure was larger in rats than in human patients. Also, Leydig cell tumours are common in rats but rare in humans. Further, there is a safety margin (12 based on unbound AUC). Altogether, the Leydig cell tumours are not expected to be relevant for humans.

In an embryofoetal development study in rabbits, abortions were observed. There was no safety margin for this effect. However, it is likely that decreased blood pressure due to the pharmacological effect of vericiguat and subsequent hypoperfusion of the placenta played a role. In a pre-and postnatal development study in rats, an increased incidence of stillbirths, decreased pup survival, and a delay in balano-preputial separation were observed, with a safety margin of approximately 21. These effects are, therefore, not expected to be clinically relevant. Also, delays in incisor eruption and vaginal opening and decreased pup body weight gain were observed. These effects are also not expected to be clinically relevant (no toxicokinetic data are available at 7.5 mg/kg/day in rats, but in the embryo-foetal development study, exposure multiple for unbound AUC at 5 mg/kg/day was 9). However, this cannot be concluded with certainty because there was no dose in these studies lower than 7.5 mg/kg/day.

Bone remodelling/hyperostosis and thickened growth plate were observed in the 2-week, 4-week and 13-week rat studies. Evidence of short-term reversibility of the bone effects is limited for vericiguat because it was only evaluated in the 4-week repeated dose study. The pivotal juvenile toxicity study also included a recovery period, but doses in that study were too low to induce the bone effects. Reversibility was clearly shown in females, whereas reversibility was only shown to a limited extent in males after 2 weeks (6-8 affected animals instead of 8-9 animals, grade 1-3 instead of grade 1-5). A recovery period of 2 weeks is however, a short period of time. For riociguat, another agent of the same class, comparable effects were reversible after 5 weeks of recovery. The fact that there were no bone findings in the 26-week study and in the rat carcinogenicity study, while there were bone effects in the 2-week, 4-week and 13-week studies, indicates that normalization took place at adult age despite continuous treatment. Safety margins were 10-31 in the 3 studies with bone effects out of 5 studies in rapidly growing rats and in the juvenile studies with no bone effects, safety margins were 3-10. The exposure was lower in the pivotal juvenile toxicity study than in the pilot juvenile toxicity study or the repeated dose studies. However, there was no indication for a lower exposure at lower age in the pivotal juvenile toxicity study. These safety margins would be expected to be sufficient to start a clinical study in children/adolescents, with adequate monitoring of bone development. In case a study in very young children is intended, it is recommended to apply for scientific advice. The applicant commits to monitor bone growth in clinical trials with paediatric patients, plans to submit a PIP modification request and will apply for scientific advice when applicable. A warning was added to section 4.2 of the SmPC of Verquvo that "Undesirable effects were observed on growing bone in non-clinical studies".

There are many potential impurities that had to be checked for genotoxic alerts. It has been sufficiently demonstrated that they are not genotoxic, or not expected to be present in the final product.

Potential impurities which were considered non-genotoxic, were either negative for genotoxic alerts in both DEREK and Leadscope, or were considered non-genotoxic based on a negative Ames test, or were considered non-genotoxic because they had the same alert as vericiguat (which was non-genotoxic in the Ames test). Five potential genotoxic impurities were controlled at levels below 30% of the TTC, i.e. below 0.5 µg/day for each of these impurities. Because Verquvo is intended for chronic use, the total intake of multiple genotoxic impurities should not exceed 5 µg/day (ICH M7). For the five mentioned potential impurities each intended to be controlled below 30% of the TTC, this is indeed the case and therefore agreed. Two other genotoxic impurities are not expected to be present in the final product. The applicant performed Bacterial mutagenicity assays for these five impurities, which were all found to be negative for mutagenic potential.

ERA

The provided data indicate that vericiguat is not expected to pose a risk to the environment. The actual validation data of analytical method number 19072019FSA-01 will be provided as post-approval commitment.

2.3.7. Conclusion on the non-clinical aspects

Overall, the primary pharmacodynamic studies provided adequate evidence that vericiguat binds specifically and with high affinity to sGC, leading to concentration-dependent cGMP production. *In vivo*, the stimulation of the NO-sGC-cGMP pathway results in vasodilatation. From the pharmacokinetic point of view, mouse, rat and dog were the most relevant species for non-clinical efficacy and safety studies. After repeated exposure, systemic exposure of vericiguat increased in an approximately dose-proportional manner. Overall, the toxicology programme revealed that most of the observed effects which were observed in the repeated dose studies could be considered to be due to the pharmacological action of vericiguat. From a non-clinical perspective, the safety of vericiguat has been sufficiently evaluated.

Considering the provided data, vericiguat is not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

This application concerns Verquvo 2.5 mg, 5 mg and 10 mg film-coated tablets. Verquvo contains the active substance vericiguat (BAY1021189; MK-1242), an orally administered stimulator of soluble guanylate cyclase (sGC). Verquvo is intended for the treatment of symptomatic chronic heart failure in adult patients with ejection fraction less than 45% who had a previous decompensation event.

The HFrEF clinical development program for vericiguat consists of the Phase 3 study, VICTORIA (Study 16493, P001), the Phase 2b dose-finding study SOCRATES-REDUCED (Study 15371, P002), and 28 Phase 1 studies. Supportive safety data from 2 studies in HFpEF are also provided (SOCRATES-PRESERVED, Study 15829, P003) and (VITALITY Study 19334, P032). This program characterizes vericiguat's biopharmaceutical, PK/PD, ADME and clinical pharmacological properties and provides clinical evidence on efficacy and safety to support the application of vericiguat for the treatment of HFrEF.

The two Phase 2b studies, SOCRATES-REDUCED (HFrEF) and SOCRATES-PRESERVED (HFpEF), included approximately 900 subjects with chronic HFrEF and HFpEF, respectively, who experienced a prior worsening HF event, with the objective of identifying an effective, well-tolerated dose for each respective patient population. These studies also contributed to the PK/PD assessment of vericiguat. An additional Phase 2 study, VITALITY, was conducted in subjects with HFpEF to further evaluate the efficacy and safety of vericiguat. As the focus of this application is the HFrEF population, the efficacy discussion of the Phase 2 studies will be limited to SOCRATES-REDUCED. The safety discussion also includes SOCRATES-PRESERVED and VITALITY.

The Phase 3 VICTORIA study evaluated the efficacy and safety of vericiguat relative to placebo in 5050 high-risk subjects with HFrEF following a worsening HF event. Data from VICTORIA also contributed to the PK/PD assessment of the compound.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

The Phase 2 and Phase 3 studies were conducted in 43 countries across Eastern and Western Europe, North America, Latin and South America, and Asia Pacific, permitting a comprehensive evaluation of patients with diverse ethnic backgrounds. An overview of the design features of the Phase 2 and Phase 3 clinical development program is provided in **Table 1.**

Table 2 summarizes the key Phase 1 studies in the clinical pharmacology program. Overall, approximately 700 healthy or symptomatic hepatic or renal impaired subjects and approximately 150 subjects with CAD were included into the clinical pharmacology studies.

Table 1. Overview of the Vericiguat Clinical Development Program

Study Number (Status) Number of Study Sites (Regions)	**Design (Indication)**	**Number of Participants by Intervention Group**	**Study Population (N)**	**Primary and Secondary Endpoint(s)**
Phase 2 Studies				
Study 15371 / P002 (completed) SOCRATES-REDUCED Module 5.3.5.1 Report PH-38448 144 sites (24 countries)	Randomized, parallel-group, placebo-controlled, double-blind, multicenter, dose-finding study Duration: 12 weeks Indication: HFrEF	Vericiguat 1.25 mg (91 randomized/91 treated/68 completed) Vericiguat 2.5 mg (91 randomized/90 treated/73 completed) Vericiguat 2.5 - 5mg (91 randomized/91 treated/67 completed) Vericiguat 2.5 – 10 mg (91 randomized/91 treated/71 completed) Placebo (92 randomized/92 treated/69 completed)	Gender: 366 M / 90 F Median age: 68.0 years Age range: 30-93 years	Primary Endpoint Change from baseline to Week 12 in log-transformed NT-proBNP.

Study Number (Status) Number of Study Sites (Regions)	**Design (Indication)**	**Number of Participants by Intervention Group**	**Study Population (N)**	**Primary and Secondary Endpoint(s)**
Study 15829 / P003 (completed) SOCRATES-PRESERVED Module 5.3.5.4 Report PH-38449 158 sites (25 countries)	Randomized, parallel-group, placebo-controlled, double-blind, multicenter, dose-finding study Duration: 12 weeks Indication: HFpEF	Vericiguat 1.25 mg (96 randomized/96 treated/82 completed) Vericiguat 2.5 mg (96 randomized/95 treated/82 completed) Vericiguat 2.5 - 5mg (96 randomized/95 treated/76 completed Vericiguat 2.5 – 10 mg (96 randomized/96 treated/84 completed) Placebo (93 randomized/93 treated/80 completed)	Gender: 250 M / 227 F Median age: 75.0 years Age range: 34-93 years	Primary Endpoints change from baseline to Week 12 in log-transformed NT-proBNP change from baseline to Week 12 in left atrial volume .
Study 19334/ P032 (completed) VITALITY Module 5.3.5.4 Report PH-40453 178 sites (21 countries)	Randomized parallel-group, placebo-controlled, double-blind, multicenter trial Duration: 24 weeks Indication: HFpEF	Vericiguat 10 mg (263 randomized/ 262 treated/ 218 completed) Vericiguat 15 mg (264 randomized/264 treated/ 224 completed) Placebo (262 randomized/262 treated/ 230 completed)	Gender: 404 M/ 385 F Median age: 73.0 years Age range: 45 to 95 years	Primary Change in KCCQ PLS from baseline to week 24.
Phase 3				
Study 16493 / P001 VICTORIA (completed) Module 5.3.5.1	Randomized, parallel-group, placebo-controlled, double-blind, event-driven, multicenter study	Vericiguat (2526 randomized/2519 treated) Placebo (2524	Gender: 3842 M/1208 F Median age: 69.0 Age range: 23 to 98 years	Primary Time to CV Death or HF hospitalizations Secondary Time to CV death Time to first HF hospitalization

Study Number (Status) Number of Study Sites (Regions)	Design (Indication)	Number of Participants by Intervention Group	Study Population (N)	Primary and Secondary Endpoint(s)
Report PH-41322 694 sites (42 countries)	Indication: HFrEF	randomized/2515 treated)	Clinically stable subjects with worsening HF defined as: • NYHA Class II-IV with standard treatment for HF for ≥30 days, • HF hospitalization or IV diuretic treatment for HF at randomization, and • EF <45% at randomization.	Time to total HF hospitalizations (first and recurrent) Time to the composite of all-cause mortality or HF hospitalization Time to all-cause mortality

Table 2. Phase 1 studies of the Vericiguat Clinical Development Program

Bayer Study Number	Report Number	Merck Protocol Number	Type of Study	Vericiguat Dose (mg)	Formulation/ Condition	Subjects Exposed to Vericiguat	Subjects Exposed to Placebo
Healthy Subject PK and Initial Tolerability							
15355	PH-37029	P004	Single dose-escalation study	0.5, 1.0, 2.5, 5.0, 7.5, 10.0, 15.0	Oral solution fasted	56	13
15357	PH-37952	P006	Multiple dose-escalation study	1.25, 5.0, 10.0, 5.0 bid	IR tablet fasted	32	11
15817	PH-38476	P012	14C mass balance study	5.0	Oral solution fasted	6	0
Biopharmaceutic Studies (described in Module 2.7.1)							
15356	PH-37306	P005	Relative bioavailability study	1.25, 5.0	Oral solution fasted IR tablet fasted/fed (high-calorie, high-fat meal)	16	0
16440	PH-37657	P019	Relative bioavailability study at fed state	1.25, 2.5, 5.0, 10.0	IR tablet fed (high-calorie, high-fat meal)	16	0
17114	PH-39515	P021	Absolute bioavailability study	10.0, 20 µg IV	IR tablet fed (high-calorie, high-fat meal) IV solution	10	0

Bayer Study Number	Report Number	Merck Protocol Number	Type of Study	Vericiguat Dose (mg)	Formulation/ Condition	Subjects Exposed to Vericiguat	Subjects Exposed to Placebo
18580	PH-39598	P028	Pivotal food effect and dose proportionality study	2.5, 5.0, 10.0	IR tablet fasted/fed (high-calorie, high-fat meal)	30	0
18581	PH-40087	P031	Relative bioavailability pediatric formulation/crushed tablet study	2.5, 10.0	IR tablet fasted/fed (high-calorie, high-fat meal / regular meal)*	30	0
Intrinsic Factors (Special Populations)							
15816	PH-37944	P011	Age and gender study	5.0	IR tablet fed (regular meal)*	42	14
15840	PH-38645	P017	Hepatic impairment study	2.5	IR-tablet fed (regular meal)*	27	0
15813	PH-38785	P009	Renal impairment study	2.5	IR-tablet fed (regular meal)*	39	0
15836	PH-37442	P013	Single- and multiple-dose escalation study in Japanese subjects	1.25, 5.0, 7.5, 10.0	IR tablet fasted + fed (high-calorie, high-fat meal)	36	12
15837	PH-37362	P014	Single-dose escalation study in Asian subjects	1.25, 5.0, 10.0	IR tablet fasted	27	9
16964	PH-40150	P020	Single- and multiple-dose escalation study in Chinese subjects	1.25, 5.0, 10.0	IR tablet fed (regular and high-calorie, high-fat meal)*	34	12
Extrinsic Factors (Drug-Drug Interactions)							
15811	PH-37185	P007	Interaction with omeprazole and antacid	5	IR tablet fasted	10	0
15812	PH-37817	P008	Interaction study with ketoconazole	1.25	IR tablet fed (regular meal)*	15	0
17116	PH-38616	P023	Interaction study with mefenamic acid	2.5	IR tablet fed (regular meal)*	16	0
15815	PH-38702	P010	Interaction study with midazolam	10.0	IR tablet fed (regular meal)*	32	0
15841	PH-39190	P018	Interaction study with digoxin	10.0	IR tablet fed (regular meal)	25	0
17746	PH-39917	P026	Interaction study with rifampicin	10.0	IR tablet fed (regular meal)*	16	0

Bayer Study Number	Report Number	Merck Protocol Number	Type of Study	Vericiguat Dose (mg)	Formulation/ Condition	Subjects Exposed to Vericiguat	Subjects Exposed to Placebo
15838	PH-38592	P015	Interaction study with acetylsalicylic acid	15.0	IR tablet fasted	25	0
15839	PH-39361	P016	Interaction study with warfarin	10.0	IR tablet fed (regular meal)*	26	25
17115	PH-38794	P022	Interaction study with nitroglycerin in healthy subjects	5.0	IR tablet fed (200 mL Fresubin, ~300 kcal)	39	39
17743	PH-39419	P024	Interaction study with sildenafil	10.0	IR tablet fed (regular meal)*	16	16
17745	PH-39559	P025	Interaction study with sacubitril/valsartan	2.5	IR tablet fed (regular meal)*	16	16
17849	PH-39300	P027	Interaction study with nitroglycerin in patients with coronary artery disease (CAD)	2.5, 5.0, 10.0	IR tablet fed (regular meal)*	24	12
18582	PH-40368	P029	Interaction study with isosorbide mononitrate in CAD patients	2.5, 5.0, 10.0	IR tablet fed (regular meal)*	26	12
Studies with specific topics							
18979	PH-41049	P030	QTc study in stable CAD patients	2.5, 5.0, 10.0	IR tablet fed (regular meal)*	73	74

* Subjects received a regular meal based on site instructions to hand out comparable number of calories to each subject. Conditions in these studies are therefore considered comparable. As an orientation, a continental breakfast with approximately 400 kcal was defined in Study 18581 Study 18581, P031

All studies were performed according to GCP guidelines.

2.4.2. Pharmacokinetics

The pharmacokinetics of vericiguat have been evaluated in 28 Phase 1 studies (including 13 clinical DDI studies), three Phase 2 studies, and one phase 3 study. In addition, various population pharmacokinetic (popPK) models were developed for vericiguat based on plasma concentration data of vericiguat obtained from the clinical studies. These popPK models were used to characterise the pharmacokinetics in the heart failure population and establish exposure-response (ER) (PKPD) relationships. Exploratory PBPK models were developed to simulate the expected pharmacokinetic properties in heart failure (HF) phase II patient group and to simulate the steady-state pharmacokinetics in patients with renal and hepatic impairment and potential interactions of vericiguat. Further, the Applicant carried out a broad panel of *in vitro* studies to identify the enzymes involved in the vericiguat metabolism and investigate potential enzyme induction and inhibition and transporter inhibition by vericiguat.

Methods

A data-rich sampling scheme was implemented in all healthy subject studies to collect plasma and, when appropriate, urine samples. In studies in subjects with HFrEF, only sparse sampling schemes were

implemented to collect plasma samples to determine vericiguat. Quantitative liquid chromatography and tandem mass spectrometry (LC-MS/MS) methods were developed and validated to quantitate vericiguat in human plasma and human urine. Separate analytical methods were also established for the determination of the M-1 metabolite in human plasma and urine.

Non-compartmental methods have been used to determine the pharmacokinetic parameters of vericiguat and its M-1 metabolite. Descriptive statistics have been used.

A Phase 2/3 population pharmacokinetic (PopPK) model was developed to evaluate the pharmacokinetics of vericiguat in heart failure patients, and a Phase 1/2/3 PopPK model was developed to support the translation of the Phase 1 program data to the patient population.

The Phase 2/3 PopPK analysis utilises a one-compartment PopPK model and includes sparse sampling data from Phase 2b (SOCRATES REDUCED 15371, MK1242-002) and Phase 3 (VICTORIA 16493, MK1242-001). In **Table** the final parameter estimates of the Phase 2/3 one-compartment PopPK model are listed.

Given the availability of dense PK sampling data, the Phase 1/2/3 PopPK model for the combined HFrEF and healthy volunteer data was a two-compartment model and includes data from Phase 1 studies (Study 15816, MK1242-011; Study 17743, MK1242-024; and Study 18580, P028MK1242), and also data from the Phase 2b (SOCRATES REDUCED 15371, MK1242-002) and Phase 3 studies (VICTORIA 16493, MK1242-001). In **Table 4** the final parameter estimates of the Phase 1/2/3 two-compartment PopPK model are listed.

As can be observed in **Table 3** and **Table 4**, the final parameter estimates of the Phase 2/3 and Phase 1/2/3 models are similar. The estimated volume of distribution from the Phase 2/3 one-compartment PopPK model was similar to the estimated sum of central volume of distribution (Vc) and peripheral volume of distribution (Vp) and the overall clearance in a similar range for the two models. In the Phase 1/2/3 PopPK model, an additive shift in Log VC by health status was observed.

Table 3. Final parameter estimates phase 2-3 one-compartment PopPK model R-13341

Table 13. Parameter Estimates and Standard Errors From the Final Population Pharmacokinetic Model for Vericiguat Plasma Concentrations

	Final Parameter Estimate		Magnitude of Interindividual Variability[a]	
Parameter	**Population Mean**	**%RSE**	**Final Estimate**	**%RSE**
CL/F: Apparent Clearance (L/h)	1.09	1.61	33.9 %CV	5.00
CL/F: Exponent of (WEIGHTBL/77.6) for CL/F	0.632	5.54		
V_c/F: Apparent Central Volume of Distribution (L)	46.8	3.48	35.5 %CV	21.3
V_c/F: Exponent of (WEIGHT/77.6) for V_c/F	0.654	11.9		
k_a: First-Order Absorption Rate Constant (1/h)	1.62	11.5	51.1 %CV	44.5
F1: Relative Bioavailability for 2.5-mg Dose Group	1.00	FIXED	NE	NA
F1: Additive Shift in Log F1 for 5-mg Dose Group	-0.178	11.1		
F1: Additive Shift in Log F1 for 10-mg Dose Group	-0.320	6.05		
cov(IIV in V_c/F, IIV in CL/F)[b]	0.0220	41.4	NA	NA
CCV RV Component	0.117	3.23	For F range of 1 to 50 ng/mL, %CV ranged from 463% to 35.4%[c]	NA
Additive RV Component	21.3	39.5		
Minimum Value of the Objective Function = 75619.553				

Table 4. Parameter Estimates and Standard Errors From the Phase 1/2/3 two-Compartment popPK Model

	Final Parameter Estimate Population		Magnitude of Interindividual Variability	
Parameter	**Mean**	**%RSE**	**Final Estimate**	**%RSE**
CL: Central Clearance (L/h)	1.17	1.62	32.0 %CV	5.28
CL: Exponent of (WEIGHTBL/76.6) for CL	0.535	6.40	32.0 %CV	5.28
CL: Exponent of (AGE/68) for CL	-0.344	10.9	32.0 %CV	5.28
VC: Central Volume (L)	27.2	3.53	27.4 %CV	16.2
VC: Additive Shift in Log VC for HFSTATUS = 1	0.396	11.1	27.4 %CV	16.2
VC: Exponent of (WEIGHTBL/76.6) for VC	0.649	10.9	27.4 %CV	16.2
Q: Intercompartmental Clearance (L/h)	0.398	8.84		
VP: Peripheral Volume (L)	13.2	7.20		
KA: First-order Absorption Rate Constant (1/h)	0.768	7.82	76.4 %CV	14.3
KA: Fold-Change in KA for PCFAST = 0	4.28	18.0		
F1: Relative Bioavailability (-)	1.00	FIXED		
F1: Fold-Change in F1 for PCFAST = 0	0.795	7.90		
F1: Additive Shift in Log F1 for DOSE2 = 1	-0.137	11.1		
F1: Additive Shift in Log F1 for DOSE3 = 1	-0.190	10.7		
cov(IIV in VC, IIV in CL)	0.0328	24.1	NA	NA
Constant CV RV component	0.140	2.88	37.4 %CV	NA
Additive RV component	0	FIXED		

Minimum value of the objective function = 102815.792

Abbreviations: %CV, coefficient of variation expressed as a percent; %RSE, relative standard error expressed as a percent; IIV, inter-individual variability; NA, not applicable; NE, not estimated. PCFAST is 0 when subjects are fasted, 1 when fed; popPK, population pharmacokinetics; RV, residual variability.

The residual variability (%CV) was calculated using the following equation: (SQRT(power(F,2)*0.140+0)/F)*100.

The calculated correlation coefficient (r) associated with cov(IIV in VC, IIV in CL) was 0.375 with $r^2 = 0.140$.

Physical-chemical properties

Vericiguat is a poorly soluble compound with high permeability. Therefore, vericiguat can be categorised as a BCS class II drug. Vericiguat solubility is pH-dependent and decreases with increasing pH.

Absorption

Following oral administration, vericiguat was rapidly absorbed; under fasting conditions, vericiguat exhibited a t_{max} of about 1 to 2 hours. When the vericiguat IR tablet is administered with food, the median t_{max} is approximately 4 h. The bioavailability of vericiguat increases when taken with food. For the 10 mg tablet, the maximum concentration (C_{max}) and the exposure (AUC) both increase by approximately 40% and administration with food reduces the variability. The bioavailability of vericiguat was comparable after administration of 10 mg IR tablet with a low-fat, high-carbohydrate meal (approximately 400 kcal) or a high-fat, high-calorie meal. Vericiguat has a high (93%) absolute oral bioavailability when taken with food.

Throughout vericiguat development, the same IR tablet formulations have been used without major modifications; therefore, no bioequivalence studies have been conducted. Exposure (AUC) and peak plasma levels (Cmax) of vericiguat administered orally as a crushed tablet in water are comparable to that of a whole tablet.

Consistent pharmacokinetics were observed across the investigated dose range (single doses of 0.5 to 15 mg and multiple doses of 1.25 to 10 mg for 7 days). In healthy volunteers, vericiguat exhibited dose-proportional pharmacokinetics and in a slightly less than dose-proportional fashion in subjects with HFrEF.

Vericiguat pharmacokinetics appear to be time-independent. In healthy subjects accumulation of vericiguat was around 150 to 170% after 7 days of qd dosing with a terminal half-life of 20-25 h. In

subjects with HFrEF, vericiguat steady state was achieved in approximately 6 days, with a terminal half-life of approximately 30 hours. This supports daily dosing.
The mean simulated steady-state population pharmacokinetic parameters of vericiguat in heart failure patients are summarised in Table **5**. The Phase 2-3 PopPK model was used for these simulations.

Table 5. Phase 2-3 population pharmacokinetic study 20964-r-13341; model based steady state geometric mean (CV%) plasma pharmacokinetic (PK) parameters of 2.5 mg, 5 mg, or 10 mg vericiguat in heart failure patients (N=2,321)

PK Parameters	2.5 mg	5 mg	10 mg
C_{max} (µg/L)	120 (29.0)	201 (29.0)	350 (29.0)
AUC (µg•h/L)	2,300 (33.9)	3,850 (33.9)	6,680 (33.9)

Distribution

The *in vitro* plasma protein binding of vericiguat is high (~97.8%) and is mainly to albumin. The blood-to-plasma ratio is 0.656, indicating that vericiguat does not specifically distribute to erythrocytes.
The vericiguat volume of distribution at steady-state in healthy subjects is ~44 L, which is close to the total volume of body water, indicating limited tissue distribution. The volume of distribution appears to be consistent between healthy subjects and HFrEF patients as population PK model parameters had a similar order of magnitude. The apparent volume of distribution following oral administration of vericiguat with food was approximately 47 L for HFrEF subjects.

Metabolism and Elimination

Metabolism
After oral administration, vericiguat is mainly metabolised to M-1, an inactive glucuronide metabolite of vericiguat (~72% AUC in plasma). Around 28% is present as a parent compound in plasma. UGT1A1 and UGT1A9 are the main UGTs involved in the conjugation. UGT1A1 and 1A9 are highly expressed in the liver and UGT1A9 in the kidney and therefore, the metabolism occurs both in the liver and kidney. Only a small fraction (<5%) of vericiguat is metabolised by CYP enzymes to M-15 which is not detected in plasma.

Excretion
The ADME study indicated that around half of the radioactivity is eliminated via urine (53%) and the other half via faeces (45%). Elimination via urine is mainly as M-1, but as vericiguat in faeces. Based on the mass balance data in combination with the high absolute bioavailability of vericiguat of 93%, the elimination of vericiguat in faeces is most likely due to excretion of M-1 into bile followed by deconjugation back to vericiguat in the intestine microflora and is not representing an unabsorbed fraction or direct excretion of the parent compound. The excretion profile is summarised in the **Table 6** below.

Table 6. Metabolite profile as percentage of dose following an oral dose of 5 mg [^{14}C]-vericiguat (study 15817)

metabolite	urine (0-288 h)	faeces (0-288 h)
vericiguat	9.0%	42.6%
M-1	40.8%	-
M-15	1.91%	1.61%
unknown	0.95%	0.99%
total	53.1%	45.2%

In healthy subjects, the inactive metabolite M-1 reaches peak plasma concentrations approximately 24-36 h after vericiguat administration. The terminal half-life of metabolite M-1 appears to be longer (53 h)

than the parent compound (approx. t½=20 h) in plasma. Renal clearance of M-1 was found slightly higher than in the parent compound with geometric mean values of 0.132 L/h (vericiguat) and 0.198 L/h (M-1), respectively.

Transporters

Based on the *in vitro* studies, vericiguat is a substrate of intestinal efflux transporters, P-glycoprotein (P-gp/ABCB1) and breast cancer resistance protein (BCRP/ ABCG2). Vericiguat is not a substrate of OATP1B1, OATP1B3, OAT1, OAT3, OCT1, and OCT2. Most likely, the transporters are saturated at the clinical dose since the absolute oral bioavailability is ~93%. Vericiguat elimination is via urine, and metabolism occurs in the kidney, but active renal uptake does not play a role.

Variability

The intra- and interindividual variability of vericiguat was assessed in healthy volunteers by means of non-compartmental analyses. Inter-individual variability of vericiguat in HFrEF patients was investigated by means of population PK, in the Phase 2/3 popPK model and the Phase 1/2/3 popPK model. Across studies, vericiguat exposure exhibits low intra-individual variability (AUC geoCV 11-15%) in healthy volunteers and low-to-moderate interindividual variability (AUC geoCV 20-34%) in heart failure patients.

Pharmacokinetics in the target population

In the phase 1/2/3 PopPK model, health status was identified as a relevant covariate on the volume of distribution (Vc/F). Health status was not a significant covariate on CL/F, suggesting that when accounting for age and body weight, AUC is expected to be similar between healthy and HF patients. Thus, the about 20% higher simulated AUC in heart failure patients than healthy volunteers from the Phase 1/2/3 PopPK analysis is primarily due to age and body weight differences between healthy volunteers and HF patients**. Table7** presents steady state AUC_{0-24} following the simulated administration of a 10 mg dose, healthy volunteer versus HFrEF Patient, using the Phase 1/2/3 PopPK model.

Table 7. Summary of the Phase 1/2/3 popPK Model Based Estimated Geometric Mean, Geometric Mean Ratio, and 90% CI for the Steady State AUC0 24 Following the Simulated Administration of a 10 mg Dose, Healthy Volunteer vs HFrEF Patient

Exposure Measure (unit)	Population	n	Geo.Mean [90% CI]	GMR [90% CI]
AUC_{0-24} (µg·h/L)	REF: Healthy subjects [a]	88	5965 [5640; 6308]	NA
	HF patients	2321	7014 [6938; 7090]	1.18 [1.11; 1.24]

Abbreviations: AUC_{0-24}, area under the plasma concentration-time curve from time 0 to 24 hours; CI, confidence interval; Geo.: geometric; GMR: geometric mean ratio; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; n, number of subjects; NA, not applicable; popPK, population pharmacokinetics; REF, reference.

a Healthy subject group includes subjects from Phase 1 studies and heart failure patient group includes subjects from Phase 2 and Phase 3 studies.

Special populations

Genetic polymorphisms

Vericiguat is mainly metabolised to M-1 and UGT1A1 and UGT1A9 are the main UGTs involved in the conjugation. UGT1A1 and UGT1A9 have known polymorphisms, but the effect of potentially relevant genetic polymorphisms on the PK of vericiguat is unknown.

Renal impairment

The applicant evaluated the use of vericiguat in patients with different stages of renal impairment (study 15813, P009) and using a PopPK model (20964-r-13341). The pharmacokinetics of vericiguat have not been studied in patients with eGFR <15 mL/min/1.73 m^2 at treatment initiation or on dialysis. In study

15813, P009 vericiguat exposure (AUC) was increased in patients with mild, moderate and severe renal impairment by 1.4-, 1.7-, and 2.2– fold, respectively, compared to patients with normal renal function. In the PopPK study 20964-r-13341, renal function was not identified to be a significant covariate in subjects with HFrEF. In this population PK study patients with moderate and severe renal impairment, the mean exposure (AUC) of vericiguat was increased by 13% and 20%, respectively, compared to patients with normal renal function. In the placebo controlled Victoria phase III study, the majority of patients with renal impairment received the target dose of 10 mg. Of the subjects with mild renal impairment 83% received the target dose, 80% of the subjects with moderate renal impairment and 75% of the subjects with severe renal impairment, regardless of the treatment. There appears to be a slight decrease in subjects treated with the target dose with decreasing renal function, but this was not statistically significant.

Hepatic impairment

Hepatic impairment was not evaluated in the population PK model in subjects with HFrEF. The applicant evaluated the pharmacokinetics of vericiguat in patients with mild and moderate hepatic impairment in dedicated phase 1 study 15840, P017. In subjects with mild hepatic impairment (Child-Pugh A) the mean exposure (AUC) to vericiguat was 21% higher compared to healthy subjects with normal hepatic function and in subjects with moderate hepatic impairment (Child-Pugh B), mean exposure to vericiguat was approximately 47% higher compared to their healthy subjects with normal hepatic function. Vericiguat has not been studied in subjects with severe hepatic impairment (Child-Pugh C). The main reason for excluding subjects with severe hepatic impairment from VICTORIA was not due to potential or expected safety issues, but due to the subjects' comorbidity and limited concomitant HF medications.

Although no relevant changes in pharmacokinetics were observed in patients with mild and moderate hepatic impairment, a considerable effect of severe hepatic impairment cannot be excluded. Glucuronidation is the main route of metabolism of vericiguat, and in patients with severe hepatic impairment, glucuronidation is commonly affected, while it usually remains normal or only mildly affected in subjects with mild and moderate hepatic impairment. Therefore, it cannot be excluded that severe hepatic impairment affects the PK of vericiguat.

The formation and elimination of the inactive glucuronide M-1 were affected by hepatic impairment. No estimate of the M-1 clearance could be provided as the sampling period was too short for a reliable estimate of the M-1 half-life. Model-simulated steady exposure of M-1 (AUCtau) was approximately 2-fold higher in subjects with mild and moderate impairment compared to subjects with normal hepatic function. This higher M1 level has been used in the assessment of potential interactions.

Gender

Although gender was not a statistically significant covariate in the PopPK analysis in subjects with HFrEF, the exposure of vericiguat was approximately 20% higher in female subjects with HFrEF relative to male subjects with HFrEF mainly attributed to differences in body weight. (Study 20964-r-13341). The effect of gender was also evaluated in study 15816, p011. In this study geometric mean Cmax and AUC values were substantially greater (32%, and 37%, respectively) in female subjects relative to male subjects.

Race

Based on a PopPK analysis (Study 20964-r-13341), race did not have a clinically meaningful effect on the pharmacokinetics of vericiguat. When corrected for bodyweight, any differences almost disappeared.

Age

Vericiguat is indicated for adult patients and has been investigated in elderly subjects. The number of elderly patients included in the PK trials is presented in **Table 8**. In dedicated clinical studies, a small non clinically relevant age effect has been observed. When differences in body weight were taken into

account an increase of about 7-8% for $C_{max,norm}$, about 14-22% for AUC_{norm} in older versus young subjects have been observed.

Table 8. Vericiguat studies with PK data for subjects aging 65 years and older

	Age 65-74 years (n / N)	Age 75-84 years (n / N)	Age 85+ years (n / N)
Clinical studies in healthy volunteers			
Age & Gender (15816)	23 / 56	8 / 56	1 / 56
Renal impairment (15813) [a]	16 / 39	5 / 39	0 / 39
Hepatic impairment (15840) [a]	4 / 27	1 / 27	0 / 27
Pooled Phase 1 PK analysis (20191) [b]	22 [c] / 899	5 [d] / 899	1 [e] / 899
Clinical studies in CAD patients			
Short-acting nitrate interaction (17849) [f]	13 / 36	1 / 36	0 / 36
Long-acting nitration interaction (18582) [f]	21 / 41	2 / 41	0 / 41
QT study (18979) [f]	37 / 74	3 / 74	0 / 74
PopPK analyses in HFrEF patients			
PopPK/PD analysis of SOCRATES-REDUCED (17401) [f]	110 / 363	97 / 363	22 / 363
Integrated PopPK analysis of SOCRATES-REDUCED and VICTORIA (20964) [f]	761 / 2321	598 / 2321	137 / 2321

Abbreviations: CAD, coronary artery disease; HFrEF, heart failure with reduced ejection fraction; HV: Healthy volunteer; n, number of older subjects; N, number of total subjects; PD, pharmacodynamics; PK, pharmacokinetics; popPK, population pharmacokinetics;

a: only healthy volunteer control group included in PK pool

b: The number of subjects in the PK pool differs from the individual studies because only healthy volunteers who received at least one dose of vericiguat were included. The number of analyzed subjects might differ for the analysis of different characteristics as the analyses were restricted to specific formulation groups and food statuses (Module 5.3.5.3, Report PH-41482, 20191 SAP)

c: N=22 consists of 18, 3 and 1 subjects from studies 15816, 15813, 15840, respectively

d: N=5 consists of 5 subjects from 15816

e: N=1 consists of 1 subject from 15816

f: not included in HV PK pool

In the Phase 1/2/3 PopPK and the Phase 2/3 PopPK studies, age had a limited impact on the exposure of vericiguat, using subjects <65 years as a reference group. The exposure ($AUC_{0-24h, ss}$) increased by 12% and 31% in subjects aged 65 to 75 years and subjects aged 75 years and older.
Vericiguat was not studied in paediatric patients.

Weight

In PopPK analysis, body weight is the main intrinsic factor influencing vericiguat exposure. Body weight was a statistically significant covariate on both apparent clearance and volume of distribution (Population study 20964, 05D7T5 and R-13340). The steady-state AUC values were approximately 27% higher in subjects with HFrEF with a body weight < 60 kg and approximately 20% lower in subjects with HFrEF with a bodyweight > 90 kg, compared to subjects with HFrEF with a body weight between 60 to 90 kg. As the impact of these covariate effects on vericiguat pharmacokinetics were deemed small in magnitude, no dose adjustment was recommended.

Pharmacokinetic interaction studies

Potential for drug-drug interactions with vericiguat and its metabolite has been investigated *in vitro* and *in vivo*.

Victim

Effect of other medicinal products on the PK of vericiguat are summarised in **Table 9** PK-interactions. Vericiguat is metabolised by UGT1A1 and UGT1A9 to M-1. Furthermore, vericiguat is a substrate of P-glycoprotein and BCRP; however, at clinical dosages, bioavailability is not reduced by P-glycoprotein and BCRP.

In a clinical study, a strong CYP3A inhibitor (ketoconazole), a weak to moderate UGT1A9 inhibitor (mefenamic acid) and a strong inducer (rifampicin) did not have a significant effect on the PK of vericiguat. Since vericiguat is glucuronidated by UGT1A1 and 1A9, a strong UGT1A1 or 1A9 inhibitor or a general UGT inhibitor of these 2 isozymes may affect the exposure to vericiguat.

In line with vericiguat solubility characteristics, medicinal products that affect the gastric pH (antacid and omeprazole) had a decreased exposure of vericiguat (~50% reduction in C_{max} and ~30% reduction in AUC). However, this decrease is not clinically relevant. Furthermore, these studies were performed under fasted conditions, and vericiguat is recommended to be taken under fed conditions, in which case the gastric pH is higher.

The frequently co-administered medicinal products acetylsalicylic acid, warfarin, sildenafil, sacubitril/valsartan (Entresto) and digoxin did not affect the PK of vericiguat.

Table 9. Effect of other medicinal products on the PK of vericiguat

vericiguat dose	perpetrator drug	C_{max} effect	AUC effect	study
1.25 mg	ketoconazole (strong CYP3A4 inhibitor)	1.11	1.13	15812
2.5 mg	mefenamic acid (UGT1A9 inhibitor)	0.97	1.20	17116
10 mg	rifampicin (strong PXR inducer)	0.91	0.71	17746
5 mg	antacid (gastric pH modifier)	0.54	0.73	15811
5 mg	omeprazole (gastric pH modifier)	0.50	0.68	15811
15 mg	acetylsalicylic acid (frequently co-administered)	0.93	0.95	15838
10 mg	warfarin (frequently co-administered)	1.03	1.03	15839
10 mg	sildenafil (frequently co-administered)	0.91-1.01	0.96-1.00	17743
2.5 mg	sacubitril/valsartan (frequently co-administered)	0.91	0.93	17745
10 mg	digoxin (frequently co-administered)	1.01	0.98	15841

Perpetrator

In vitro, vericiguat is not a direct and time-dependent inhibitor of CYPs at maximal systemic concentration and not of CYP3A at maximal intestinal concentrations. In addition, vericiguat is not an inhibitor of UGTs at clinically relevant concentrations. Vericiguat is not an inhibitor of P-glycoprotein, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, BSEP, MATE1 and MATE2-K at maximal systemic concentrations. Besides, vericiguat is not an inhibitor of OATP1B1, OATP1B3 and OCT1 at maximal portal

vein concentrations. Furthermore, vericiguat is not an inhibitor of P-glycoprotein and BCRP at maximal intestinal concentrations. Vericiguat is not an inducer via PXR at maximal intestinal concentrations (<10 µM) and not of AhR, CAR and PXR at maximal systemic concentrations.

The effect of vericiguat on the PK of other medicinal products is summarised in **Table 10**. In clinical DDI studies, no effects were observed of vericiguat on the PK of a substrate of CYP3A (midazolam) and a substrate of CYP2C9 (S-warfarin), which is in line with the *in vitro* study results.

Frequently co-administered medicinal products (sildenafil, sacubitril, valsartan, and digoxin) were not affected when co-administered with vericiguat.

Table 10. Effect of vericiguat on the PK of other medicinal products.

vericiguat dose	victim drug	C_{max} fold increase	AUC fold increase	study
10 mg	midazolam (CYP3A4 substrate)	0.77	0.82	15815
10 mg	S-warfarin (CYP2C9 substrate)	0.98	0.98	15839
10 mg	sildenafil (frequently co-administered)	1.14-1.20	1.13-1.22	17743
2.5 mg	sacubitril (frequently co-administered)	1.19	1.04	17745
2.5 mg	valsartan (frequently co-administered)	1.03	1.03	17745
10 mg	digoxin (frequently co-administered)	1.00-1.04	1.04	15841

Footnote: For digoxin, CTrough was assessed (not CMax)

2.4.3. Pharmacodynamics

Mechanism of action

Heart failure (HF) is associated with impaired synthesis of NO and decreased activity of its receptor, soluble guanylate cyclase (sGC). sGC catalyses the synthesis of concentration-dependent cyclic guanosine monophosphate (cGMP), an important signalling molecule that regulates critical physiological processes such as cardiac contractility, vascular tone, and cardiac remodelling. Deficiency in sGC-derived cGMP contributes to myocardial and vascular dysfunction.

Vericiguat restores the relative deficiency in this signalling pathway by directly stimulating sGC, independently of and synergistically with NO, to augment the intracellular cGMP levels, which may improve both myocardial and vascular function. Therefore, the complementary cardiovascular benefits of vericiguat in heart failure patients are attributed to the active restoration of the deficient NO-sGC-cGMP pathway driving heart failure progression.

Primary and Secondary pharmacology

Primary Pharmacology

The pharmacodynamic effects of vericiguat were evaluated after single and multiple-dose administration in healthy subjects.

Study 15355 was a single-blind, randomized, placebo-controlled, single- dose-escalation phase 1 study to investigate the safety and tolerability of vericiguat after single oral doses of 0.5, 1, 2.5, 5, 7.5, 10, and 15 mg or placebo administered as polyethylene glycol solution in 69 healthy male subjects in a fasted state. The secondary objectives of this study were to investigate the pharmacodynamics and pharmacokinetics of vericiguat.

Impedance cardiography showed an overall significant effect of vericiguat on the change in heart rate, cardiac output, cardiac index, and systemic vascular resistance (SVR) from baseline of differences of profile days (Day 1 minus Day -1) up to 4 hours (Table 1**1**). No such effect on stroke volume was detected. Further, there was an overall significant effect of vericiguat on the change in heart rate over 1 min from baseline of differences of profile days (Day 1 minus Day -1) up to 4 hours (Table 1**2**).

Table 21. LS-means with 95% confidence intervals for the treatment effects on impedance cardiography parameters: change from baseline of differences of profile days up to 4 hours (all subjects valid for PD)

Parameter	*P* value of F statistic of		Treatment	Difference	95% confidence limits		*P* value of
	treatment	treatment*time		(active-placebo)	Lower	Upper	T statistic
Stroke volume (mL)	0.3687	0.2546	0.5 mg (non-smokers)	-1.95	-7.08	3.19	0.4515
			1.0 mg (non-smokers)	-2.56	-7.46	2.35	0.3011
			2.5 mg (non-smokers)	-1.26	-6.22	3.70	0.6125
			5.0 mg (non-smokers)	0.44	-4.67	5.56	0.8625
			5.0 mg (smokers)	1.61	-3.77	6.99	0.5509
			7.5 mg (non-smokers)	3.44	-1.43	8.30	0.1627
			10.0 mg (non-smokers)	0.53	-4.35	5.41	0.8276
			15.0 mg(non-smokers)	3.87	-2.32	10.06	0.2160
Heart rate (BPM)	<0.0001	0.3240	0.5 mg (non-smokers)	-1.72	-4.54	1.10	0.2276
			1.0 mg (non-smokers)	-0.90	-3.67	1.87	0.5186
			2.5 mg (non-smokers)	-0.95	-3.66	1.75	0.4837
			5.0 mg (non-smokers)	2.85	0.01	5.69	0.0489
			5.0 mg (smokers)	1.22	-1.74	4.18	0.4137
			7.5 mg (non-smokers)	2.69	-0.01	5.38	0.0510
			10.0 mg (non-smokers)	2.25	-0.45	4.94	0.1008
			15.0 mg (non-smokers)	8.91	5.49	12.33	<0.0001
Cardiac output (L/min)	0.0008	0.1117	0.5 mg (non-smokers)	-0.29	-0.73	0.16	0.1992
			1.0 mg (non-smokers)	-0.25	-0.67	0.17	0.2422
			2.5 mg (non-smokers)	-0.10	-0.52	0.33	0.6480
			5.0 mg (non-smokers)	0.23	-0.21	0.66	0.3005
			5.0 mg (smokers)	0.19	-0.27	0.65	0.4096
			7.5 mg (non-smokers)	0.38	-0.04	0.79	0.0767
			10.0 mg (non-smokers)	0.19	-0.22	0.61	0.3572
			15.0 mg (non-smokers)	1.04	0.51	1.57	0.0002

Parameter	*P* value of F statistic of		Treatment	Difference	95% confidence limits		*P* value of
	treatment	treatment*time		(active-placebo)	Lower	Upper	T statistic
Cardiac index (L/min/m^2)	0.0009	0.1122	0.5 mg (non-smokers)	-0.14	-0.36	0.08	0.2119
			1.0 mg (non-smokers)	-0.12	-0.33	0.09	0.2623
			2.5 mg (non-smokers)	-0.05	-0.26	0.17	0.6504
			5.0 mg (non-smokers)	0.10	-0.12	0.32	0.3467
			5.0 mg (smokers)	0.11	-0.12	0.34	0.3492
			7.5 mg (non-smokers)	0.20	-0.01	0.41	0.0626
			10.0 mg (non-smokers)	0.10	-0.11	0.31	0.3567
			15.0 mg (non-smokers)	0.53	0.26	0.79	0.0002
Systemic vascular resistance (mmHg * min/L)	0.0068	0.4569	0.5 mg (non-smokers)	1.16	-0.99	3.30	0.2859
			1.0 mg (non-smokers)	1.26	-0.77	3.30	0.2181
			2.5 mg (non-smokers)	0.88	-1.20	2.95	0.4008
			5.0 mg (non-smokers)	-0.48	-2.59	1.62	0.6485
			5.0 mg (smokers)	-0.74	-2.97	1.49	0.5072
			7.5 mg (non-smokers)	-2.51	-4.52	-0.49	0.0155
			10.0 mg (non-smokers)	-0.81	-2.83	1.21	0.4264
			15.0 mg (non-smokers)	-3.12	-5.68	-0.56	0.0180

Table 32. LS-means with 95% confidence intervals for the treatment effects on heart rate over 1 minute: change from baseline of differences of profile days up to 4 hours (all subjects valid for PD) baseline of differences of profile days up to 4 hours (all subjects valid for PD)

Parameter	*P* value of F statistic of		Treatment	Difference	95% confidence limits		*P* value of
	treatment	treatment*time		(active - placebo)	Lower	Upper	T statistic
Heart rate over 1 minute (BPM)	<0.0001	0.0209	0.5 mg (non-smokers)	-1.17	-4.27	1.94	0.4552
			1.0 mg (non-smokers)	-1.01	-4.03	2.01	0.5076
			2.5 mg (non-smokers)	-1.01	-3.99	1.96	0.4984
			5.0 mg (non-smokers)	3.66	0.56	6.77	0.0215
			5.0 mg (smokers)	1.27	-1.99	4.54	0.4380
			7.5 mg (non-smokers)	3.39	0.41	6.36	0.0263
			10.0 mg (non-smokers)	2.93	-0.08	5.93	0.0559
			15.0 mg(non-smokers)	9.62	5.81	13.42	<0.0001

Vasoactive hormones were investigated as indicators of important blood pressure control mechanisms and demonstrated the extent of compensation to the vasodilative effect. cGMP represents the second messenger of the target enzyme sGC and reflects the increased target activity by vericiguat. There was an overall significant effect of vericiguat on the change in plasma cGMP, noradrenaline, and plasma renin activity (PRA) from baseline of differences of profile days (Day 1 minus Day -1) up to 4 hours (**Table 13**). No such effect on serum aldosterone was detected. There was no overall significant effect of vericiguat on the change in any of the further biomarkers (asymmetric dimethyl arginine (ADMA), BNP, NT-proBNP, and osteopontin) from baseline of differences of profile days (Day 1 minus Day -1) up to 4 hours in healthy subjects.

Table 43. S-means with 95% confidence intervals for the treatment effects on neurohormones: change from baseline of differences of profile days up to 4 hours (all subjects valid for PD)

Parameter	*P* value of F statistic of		Treatment	Difference	95% confidence limits		*P* value of
	treatment	treatment*time		(active-placebo)	Lower	Upper	T statistic
Aldosterone (pmol/L)	0.7784	0.0442	0.5 mg (non-smokers)	-17.21	-72.60	38.18	0.5366
			1.0 mg (non-smokers)	14.74	-37.63	67.10	0.5755
			2.5 mg (non-smokers)	-10.20	-62.67	42.27	0.6987
			5.0 mg (non-smokers)	-10.36	-65.13	44.40	0.7063
			5.0 mg (smokers)	-13.03	-70.71	44.66	0.6530
			7.5 mg (non-smokers)	3.32	-49.13	55.77	0.8997
			10.0 mg (non-smokers)	27.65	-25.69	80.98	0.3038
			15.0 mg (non-smokers)	31.84	-34.85	98.53	0.3433
cGMP (nmol/L)	0.0310	0.9031	0.5 mg (non-smokers)	0.88	-1.01	2.76	0.3567
			1.0 mg (non-smokers)	3.10	1.23	4.97	0.0016
			2.5 mg (non-smokers)	1.16	-0.67	2.99	0.2089
			5.0 mg (non-smokers)	0.23	-1.71	2.17	0.8120
			5.0 mg (smokers)	0.02	-1.96	2.01	0.9810
			7.5 mg (non-smokers)	1.53	-0.30	3.36	0.1004
			10.0 mg (non-smokers)	1.49	-0.32	3.31	0.1039
			15.0 mg (non-smokers)	3.02	0.73	5.31	0.0106
Noradrenaline (ng/L)	<0.0001	0.9042	0.5 mg (non-smokers)	5.52	-33.05	44.09	0.7756
			1.0 mg (non-smokers)	33.60	-4.51	71.71	0.0829
			2.5 mg (non-smokers)	24.62	-12.41	61.65	0.1885
			5.0 mg (non-smokers)	54.59	14.67	94.50	0.0082
			5.0 mg (smokers)	66.72	26.01	107.42	0.0017
			7.5 mg (non-smokers)	54.27	16.66	91.87	0.0054
			10.0 mg (non-smokers)	76.73	39.62	113.84	0.0001
			15.0 mg (non-smokers)	118.35	69.96	166.75	<0.0001

Parameter	*P* value of F statistic of		Treatment	Difference	95% confidence limits		*P* value of
	treatment	treatment*time		(active-placebo)	Lower	Upper	T statistic
Plasma renin activity (ng/mL/h)	0.0021	0.4701	0.5 mg (non-smokers)	-0.05	-0.24	0.14	0.5882
			1.0 mg (non-smokers)	0.18	-0.00	0.36	0.0549
			2.5 mg (non-smokers)	0.03	-0.15	0.21	0.7319
			5.0 mg (non-smokers)	0.02	-0.16	0.21	0.7980
			5.0 mg (smokers)	0.20	-0.00	0.40	0.0520
			7.5 mg (non-smokers)	0.14	-0.04	0.32	0.1377
			10.0 mg (non-smokers)	0.30	0.12	0.48	0.0014
			15.0 mg (non-smokers)	0.39	0.16	0.62	0.0014

Study 15357 was a randomized, single-blind, placebo-controlled phase 1 multiple-dose escalation study to investigate the safety tolerability, pharmacokinetics and pharmacodynamics of vericiguat after

oral dosing of 1.25, 5, and 10 mg once a day (qd) and 5 mg twice a day (bid) over 7 days, given as a 1.25 IR tablet or multiples of 1.25 mg IR tablets, in 43 healthy subjects in the fasted state.

Significant effects of multiple vericiguat doses on the impedance cardiographic heart rate (increase), systemic vascular resistance (decrease), cardiac output (increase) and cardiac index (increases) at Day 7 were observed, without showing dependency on the dose of vericiguat (Table 14). The heart rate over 1 min derived from non-invasive measurements of vital signs showed a baseline-corrected dose-dependent increase of heart rate (LS-means) by 5 BPM (1.25 mg OD), 7 BPM (5 mg OD), 8 BPM (10 mg OD) and 5 BPM (5 mg BID) compared to placebo at Day 7. Results regarding blood pressure were inconsistent (Table 15). Additionally, there was no indication of an increased risk for orthostatic reactions after vericiguat. Concerning vasoactive hormones, noradrenaline concentrations were significantly increased in subjects taking vericiguat (10mg qd and 5 mg bid) compared to placebo at Day 7, whereas no effect on cGMP and plasma renin activity was observed.

Table 54. Study 15357, P006 - Impedance cardiography during 4 h after administration: change from baseline of difference of Day 7 and Day -1: Results of ANCOVA, PDS, n=43

Parameter	p-value of F-statistics	Treatment	LS-Mean Differences "active – placebo" [95% Confidence Interval]	p-value of t-statistics
Cardiac output (L/min)	0.0172	1.25 mg qd	0.7227 [0.25 ; 1.19]	0.0034
		5.0 mg qd	0.6999 [0.21 ; 1.19]	0.0059
		10 mg qd	0.5476 [0.07 ; 1.02]	0.0255
		5 mg bid	0.6589 [0.15 ; 1.17]	0.0133
Cardiac index (L/min/m²)	0.0223	1.25 mg qd	0.3672 [0.13 ; 0.60]	0.0032
		5.0 mg qd	0.3226 [0.08 ; 0.57]	0.0109
		10 mg qd	0.2687 [0.03 ; 0.51]	0.0283
		5 mg bid	0.3190 [0.06 ; 0.58]	0.0167
Heart rate (beats/min)	0.0229	1.25 mg qd	4.1629 [0.85 ; 7.48]	0.0153
		5.0 mg qd	3.9647 [0.55 ; 7.37]	0.0239
		10 mg qd	5.3817 [1.99 ; 8.78]	0.0027
		5 mg bid	4.1397 [0.53 ; 7.75]	0.0259
Stroke volume (mL)	0.0692	1.25 mg qd	7.2465 [1.68 ; 12.8]	0.0121
		5.0 mg qd	6.9984 [1.17 ; 12.8]	0.0199
		10 mg qd	2.0807 [-3.74 ; 7.90]	0.4735
		5 mg bid	5.1826 [-0.83 ; 11.2]	0.0889
Systemic vascular resistance (mmHg·min/L)	0.0162	1.25 mg qd	-2.7898 [-5.03 ; -0.55]	0.0160
		5.0 mg qd	-3.8351 [-6.19 ; -1.48]	0.0021
		10 mg qd	-2.6758 [-5.04 ; -0.31]	0.0277
		5 mg bid	-3.1743 [-5.61 ; -0.74]	0.0119

Note: p-value of F-statistic treatment: Test of equal treatments means.
p-value of t-statistic: Test of difference placebo-active equals zero.

Table 65. Vital signs during 4 hours after administration: change from baseline of difference of profile days- results of ANCOVA, safety analysis set, n=43

Para-meter (Unit)	Differences	P-value of F-statistics for treatment / treatment *time	Vericiguat dose (treatment group)	Difference active - placebo (LS-mean)	95% CI Lower limit	95% CI Upper limit	P-value of T-statistics
Systolic blood pressure (mmHg)	Day 1 vs Day -1	0.0075 / 0.0009	1.25 mg OD	1.8139	-1.81	5.44	0.3173
			5 mg OD	-4.5703	-8.03	-1.11	0.0111
			10 mg OD	0.1161	-3.34	3.57	0.9460
			5 mg BID	-2.9680	-6.78	0.84	0.1232
	Day 7 vs Day -1	0.0059 / 0.0668	1.25 mg OD	3.9173	-0.11	7.94	0.0560
			5 mg OD	-3.6857	-7.55	0.18	0.0609
			10 mg OD	-2.4795	-6.34	1.39	0.2017
			5 mg BID	-2.8157	-6.89	1.26	0.1701
	Day 7 vs Day 1	0.0339 / 0.4246	1.25 mg OD	4.7644	1.01	8.51	0.0142
			5 mg OD	2.7602	-1.13	6.65	0.1591
			10 mg OD	-1.3387	-5.21	2.54	0.4883
			5 mg BID	1.6372	-2.45	5.73	0.4223
Diastolic blood pressure (mmHg)	Day 1 vs Day -1	0.7971 / 0.6223	1.25 mg OD	-1.1245	-4.39	2.14	0.4894
			5 mg OD	-0.7784	-4.08	2.52	0.6358
			10 mg OD	-1.4695	-4.76	1.83	0.3720
			5 mg BID	-2.0286	-5.50	1.44	0.2435
	Day 7 vs Day -1	0.1968 / 0.5664	1.25 mg OD	2.1685	-1.68	6.01	0.2606
			5 mg OD	-1.2020	-5.21	2.81	0.5474
			10 mg OD	-2.3555	-6.44	1.73	0.2499
			5 mg BID	-2.3283	-6.50	1.85	0.2659
	Day 7 vs Day 1	0.0063 / 0.7864	1.25 mg OD	4.1219	1.20	7.04	0.0069
			5 mg OD	-0.8027	-3.83	2.23	0.5946
			10 mg OD	-1.1014	-4.16	1.96	0.4706
			5 mg BID	-1.0633	-4.26	2.14	0.5049

Secondary Pharmacology

Effect on cardiac depolarization

Supratherapeutic exposures of vericiguat, as recommended per ICH E14 Guidance (FDA 2017, ICH 2005, ICH 2015) could not be tested in a conventional thorough QT (TQT) study in healthy subjects due to safety concerns. Thus, a dedicated, randomized, placebo-controlled, double-blind, study with moxifloxacin as a positive control investigated the QT/QTc interval and proarrhythmic potential of vericiguat in subjects with stable CAD (**Study 18979**). In this study, in which vericiguat was titrated up to 10 mg at steady state (ie, to therapeutic exposures), across all timepoints the mean difference (vericiguat minus placebo) in QTcF change from baseline was <6 msec with an upper bound of the 90% CI below 10 msec. The highest mean prolongation of QTcF was 5.6833 msec (90 %CI: [1.7759 msec; 9.5908 msec]) 2 hours 30 minutes post-dose. With respect to assay sensitivity analysis, the largest difference in change from baseline with moxifloxacin within the chosen time frame was 13.5155 msec (corrected two-sided 90% CI: [10.2266 msec; 16.8045 msec]), observed at 4 hours post-dose.

Thus, administration of the vericiguat therapeutic treatment regimen titrated up to 10 mg at steady-state did not prolong the QTc interval to a clinically significant degree.

Further, in the single (**Study 15355**) and multiple (**Study 15357**) dose-escalation studies in healthy subjects receiving up to 15 mg vericiguat QD, triplicate ECGs were collected for QTc evaluation. The dedicated evaluations also did not show any potential indication for vericiguat to prolong the QTc interval compared to placebo.

In exposure-QTc analyses using centrally read ECGs obtained at trough concentrations from both vericiguat SOCRATES-REDUCED and SOCRATES-PRESERVED HF studies (**Study 15371** and **Study 15829**), the upper limit of the 90% CI for the change from baseline in QTc in the highest quartile of exposure was well below 10 msec. In addition, a correlation analysis of exposure (vericiguat concentration, Ctrough) and QTcF showed a negative correlation. All results were consistent between the two studies for both (QTcB and QTcF) corrections.

In VICTORIA (**Study 16493**), investigator-read ECGs were used to assess the impact of vericiguat on QTcF interval as a measure of QTc prolongation. At week 16, (the timepoint at which post-baseline ECGs were systematically collected and assumed steady-state on target dose was reached), there were no differences in the mean QTcF change from baseline between subjects in the vericiguat group compared with the placebo group.

Pharmacodynamic interactions with other medicinal products or substances

DDI studies assessed potential PD interactions with antithrombotics/anticoagulants (aspirin, warfarin), drugs acting on the NO-sGC-cGMP pathway (i.e., short and long-acting nitrates as well as a PDE-5 inhibitor) and other drugs commonly used in HF patients (sacubitril/valsartan).

No clinically relevant interactions were observed when vericiguat was co-administered with acetylsalicylic acid (**Study 15838**), warfarin (**Study 15839**), or sacubitril/valsartan (**Study 17745**).

Nitroglycerin

Pharmacodynamic interactions with nitroglycerin have been investigated in two clinical studies; one study in healthy subjects (Study 17115) and one study in CAD subjects (**Study 17489**).

Study 17115 was a randomized, placebo-controlled, double-blind cross-over study in 2 parallel cohorts to investigate the PD interaction between 5 mg vericiguat and 0.2 mg sublingual nitroglycerin. Although no statistical differences were found after a single dose of 5 mg vericiguat administered 12h to 4 h before a single dose of 0.2 mg nitroglycerin, a trend to a relevant decrease in SBP and DBP could be observed at time point 6 h (under fed conditions the t_{max} is 4 h). Considering that the target dose of vericiguat concerns 10 mg and the therapeutic doses of sublingual nitroglycerin tablets includes 0.3 -0.6 mg, this study only investigated subtherapeutic doses of vericiguat and nitroglycerin; consequently, a clinically relevant PD interaction could not be ruled out based on this study.

Study 17849 was a randomized, placebo-controlled, double-blind, parallel-group to investigate the PD interaction between multiple oral qd dosed of vericiguat (up-titration from 2.5 mg to 10 mg) after coadministration with 0.4 mg nitroglycerin (sublingually administered using a spray) in 36 subjects with stable CAD. No significant differences in haemodynamic parameters (SBP, DBP, and heart rate) were observed between vericiguat and placebo during coadministration with 0.4 mg nitroglycerin. However, considering that at baseline, the mean SBP was slightly higher in the vericiguat treatment group than in the placebo treatment group (127 mmHg vs. 120 mmHg) and that SBP values decreased from Day 0 to Day 41 in the vericiguat group while in the placebo treatment group, SBP remained unchanged over the course of treatment, the observed results could be biased. Therefore, firm conclusions on the absence of clinically relevant PD interactions when vericiguat and nitroglycerin were co-administered could not be made.

In VICTORIA (**Study 16493**), 269 subjects (10.8%) in the vericiguat group used nitrate at one or more visits, of which 67 subjects (2.7%) used long-acting nitrates or NO donors. These data showed no adverse events of symptomatic hypotension or syncope when vericiguat was co-administered with any nitrate use.

Isosorbide mononitrate

Study 18582 was a randomized, placebo-controlled, double-blind, parallel-group study to investigate the PD interaction (effects on BP and HR) of 2.5 mg, 5.0 mg and 10 mg vericiguat each given over 14 ± 3 days together with the long-acting isosorbide mononitrate (ISMN) 60 mg extended-release formulation after a pre-treatment phase (ISMN-starting dose: 30 mg) in 41 subjects with stable CAD (36 males and 5 females). No significant effects on BP and HR of vericiguat than placebo co-administered with 60 mg of ISMN could be observed. However, additional explorative ANCOVA analyses indicate statistically significant decreases in systolic and diastolic blood pressure of 2 to 5 mmHg and increases of 1 to 2 beats/min in heart rate when vericiguat was co-administered, which was considered not clinically relevant.

To note, long-acting nitrates were prohibited in VICTORIA, because the DDI study 18582 was conducted after enrolment of the first patient in VICTORIA.

Sildenafil

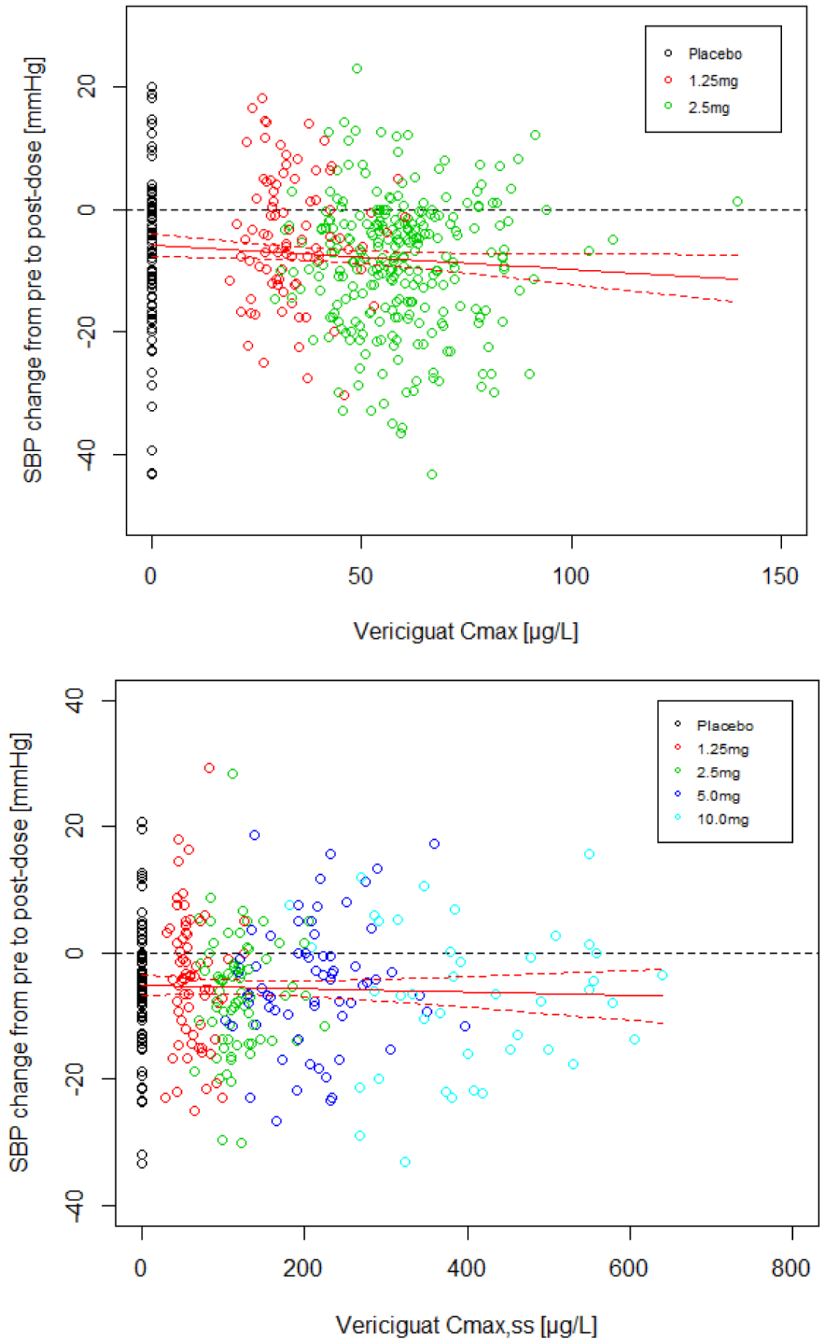
Study 17743 was a randomized, placebo-controlled, and single-blinded, group-comparison interaction study to investigate the safety, tolerability, pharmacodynamic effect and pharmacokinetics of single oral doses of 25 mg, 50 mg and 100 mg of the PDE5 inhibitor sildenafil administered after 10 mg vericiguat or placebo tablets over 16 days after a standardized meal in 32 healthy male subjects. This study demonstrated that co-administration of vericiguat with sildenafil (25 and 100 mg) resulted in significant decreases in SBP of $\leq$ 5.4 mmHg, without a trend for dose-dependency. Since this interaction study was conducted in parallel to the VICTORIA trial the use of PDE-5 inhibitors was prohibited in VICTORIA. Consequently, there is no experience with concomitant use of vericiguat and PDE-5 inhibitors in patients with HFrEF. However, because the DDI study in healthy male subjects does not suggest a safety signal and that the pharmacokinetics and pharmacodynamic effects of vericiguat differs from those of riociguat (co-administration of riociguat and PDE5 inhibitors is contraindicated), it is agreed with the Applicant that there is no sufficient data to support a contra-indication. Consequently, a recommendation not the use vericiguat in combination with PDE-5 inhibitor is stated in section 4.4 of the SmPC.

Relationship between plasma concentration and effect

Population PK/PD of subjects with HFrEF in SOCRATES-REDUCED (Study 17401)

A preliminary popPK/PD model (Study 17401) had been developed using data from SOCRATES-REDUCED. This model was then used to determine vericiguat exposures to facilitate the evaluation of the exposure-response relationship for SBP and NT-proBNP in subjects with HFrEF from SOCRATES-REDUCED. Using linear regression analysis, a C_{max}-dependent lowering of SBP after the first dose (when dosing started at 1.25 mg or 2.5 mg) was observed, but not after 8 weeks (Visit 4) of dosing (when most subjects with HFrEF had been up-titrated to 10 mg vericiguat), suggesting that titration of vericiguat up to 10 mg was performed without relevant effects on SBP Figure 2 and Table 16).

Figure 2. PK/PD Study 17401 - Correlation of vericiguat peak concentrations (Cmax, Cmax,ss) with pre- to post-dose change of SBP at visit 1 (first dose, upper panel) and visit 4 (after 8 weeks, lower panel).



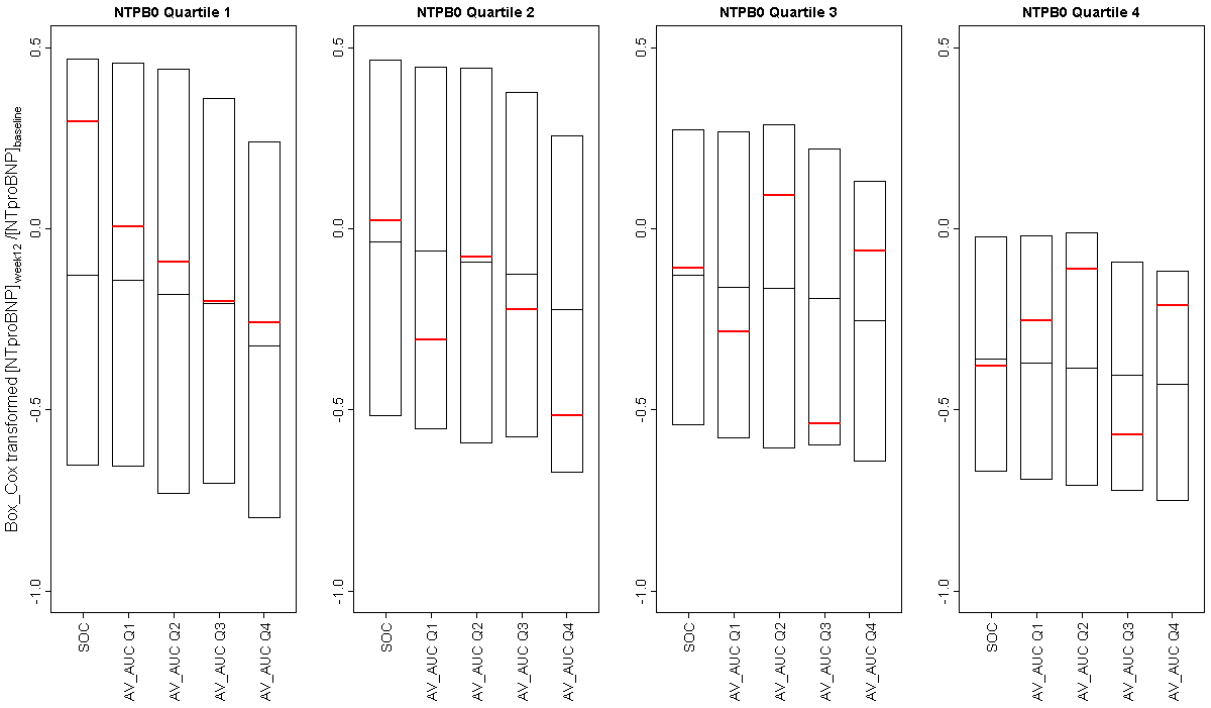
Open symbols: data from individual subjects with HFrEF belonging to different treatment arms (black: placebo, red: 1.25 mg, green: 2.5 mg, blue: 5 mg, cyan: 10 mg). Red solid line: linear regression model, dashed lines: 95% confidence interval of the regression model.

Table 76. PK/PD Study 17401, 05GJCP - Linear regression parameter table

	Visit 1	Visit 4
Intercept (SBP change from pre- to post-dose [mmHg])	-5.857 ($p < 0.001$)	-5.124 ($p < 0.001$)
Slope (vericiguat C_{max} [µg/L])	-0.039 ($p = 0.047$)	-
Slope (vericiguat $C_{max,ss}$ [µg/L])	-	-0.003 ($p = 0.528$)

Exploratory PK-PD analysis for the surrogate cardiac biomarker NT-proBNP in heart failure showed an exposure-dependent reduction of NT-proBNP by vericiguat, dependent on baseline NT-proBNP. It showed greater exposure-dependent reductions (slopes within the quartiles) in NT-proBNP in the lowest NT-proBNP quartiles (Figure 3).

Figure 3. PK/PD Study 17401, 05GJCP - Stratified boxplots showing influence of baseline NT proBNP concentration and vericiguat exposure on observed and simulated NT proBNP ratio week 12 / baseline



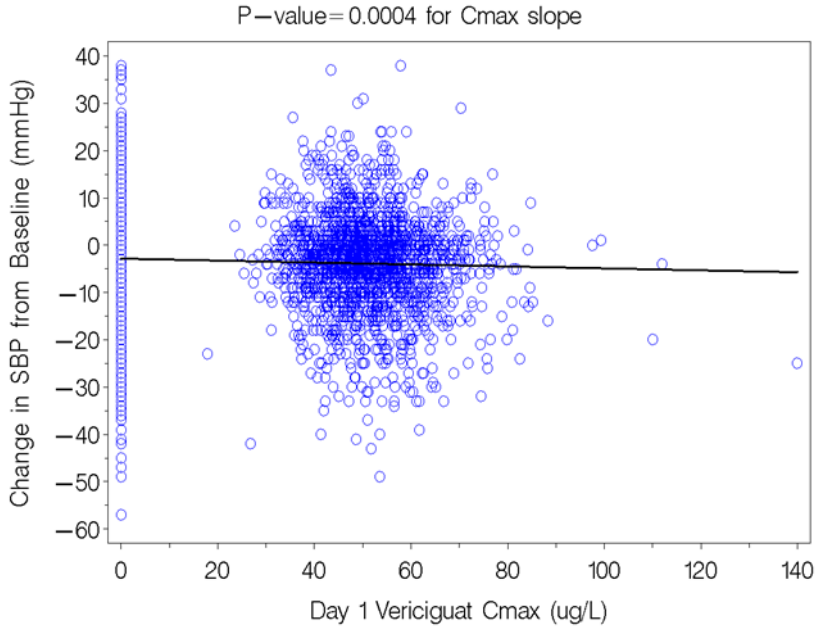
NTPB0 Quartile 1 / 2 / 3 / 4: Subjects with HFrEF assigned to first / second / third / fourth quartiles of baseline [NT-proBNP] according to fixed boundaries (1559 pg/mL, 3000 pg/mL, 6246 pg/mL)
SOC: Subjects with HFrEF treated with standard of care
AV_AUC Q1 / Q2 / Q3 / Q4: Subjects with HFrEF in first / second / third / fourth quartiles of average 24 h vericiguat AUC (week 1 to week 12) according to fixed boundaries (1403 µg·h/L, 2093 µg·h/L, 3525 µg·h/L)
Red lines: Median of observed data, Unshaded boxes: Median and 95% prediction interval of simulated data

Population PK-safety and PK-efficacy analysis of subjects with HFrEF in VICTORIA (Study 20965)

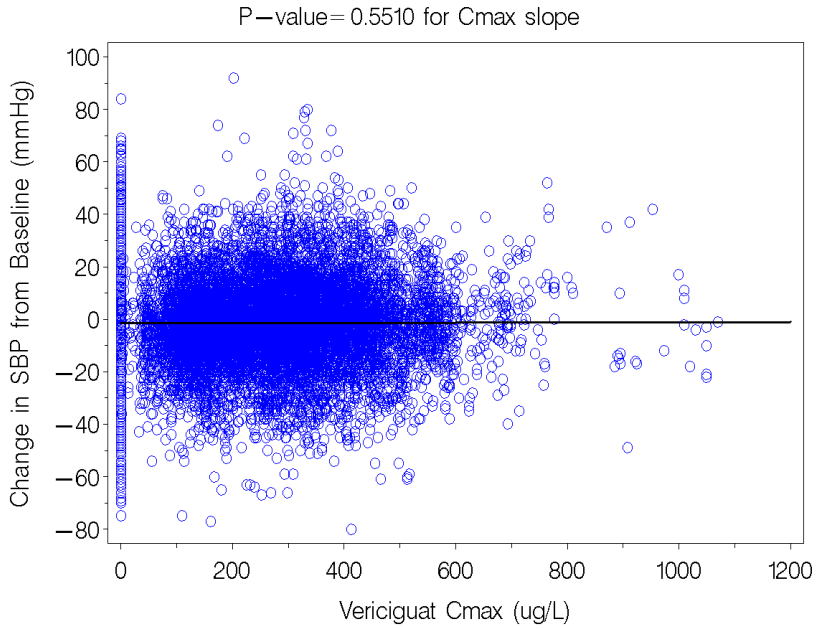
PK-safety and PK-efficacy analyses were performed to assess exposure-response relationships observed in VICTORIA. In the exposure-SBP analysis, there was a small but statistically significant correlation between higher vericiguat exposures (Cmax) and decrease in baseline in SBP 2 h post-dose on Day 1 (Figure 4). However, the change in SBP from baseline during the remaining days of the titration phase through the duration of the study was not associated with vericiguat exposure.

Furthermore, to understand the exposure-response for symptomatic hypotension and syncope in subjects on the 2.5 mg starting dose, an analysis was conducted in subjects on the 2.5 mg dose only during the first 14 days of treatment. Although subjects could have titrated to the 5 mg dose up to 4 days before or after day 14, this analysis was restricted to between days 1-14. Subjects who were not on the 2.5 mg dose during this time were censored for this analysis. The probability of symptomatic hypotension and syncope observed during the first 14 days was low and did not differ across the quartiles of vericiguat exposure (Table**17**).

Figure 4. PK/PDAE Study 20965, 05D7SZ - Correlation of the change in systolic blood pressure from baseline and vericiguat Cmax on the day of systolic blood pressure measurement (day 1 at 2 h post dose, upper panel; and over the remainder of the trial lower panel) in Victoria



The line represents a linear regression fit to the data.



The line represents a linear regression fit to the data.

Table 17. PK/PDAE Study 20965, 05D7SZ - Summary of the First ECIs of symptomatic hypotension and syncope for subjects with HFrEF in VICTORIA on the 2.5 mg dose of vericiguat during Days 1-14 grouped by quartiles of vericiguat Cmax on Day 14

			Vericiguat $C_{max,ss}$ quartile				
PD Endpoint		**Placebo**	**Q1**	**Q2**	**Q3**	**Q4**	**Overall**
Symptomatic Hypotension on Days 1 to 14							
n (%)	No Event	2491 (99.0)	468 (98.9)	480 (98.4)	487 (98.8)	501 (99.2)	4427 (98.9)
	Event	24 (1.0)	5 (1.1)	8 (1.6)	6 (1.2)	4 (0.8)	47 (1.1)

Syncope on Days 1 to 14							
n (%)	No Event	2509 (99.8)	469 (99.2)	488 (100.0)	489 (99.2)	505 (100.0)	4460 (99.7)
	Event	6 (0.2)	4 (0.8)	0 (0.0)	4 (0.8)	0 (0.0)	14 (0.3)

Exposure-PD effect analyses across different phase 1 studies in healthy volunteers (Study 15356, Study 15357, Study 15836) demonstrated greater increases in cardiac index and cardiac output and greater decreases in systemic vascular resistance at higher plasma concentrations. In contrast, no clear exposure-response concerning HR was observed.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Individual bioanalytical methods for vericiguat and its metabolite in plasma and urine were adequately validated and generally followed the guidance of the current EMA Guideline on Bioanalytical Method Validation (EMEA/CHMP/EWP/192217/2009). The LC-MS/MS methods are considered selective and suitable for the analysis of vericiguat and M - 1 in plasma and urine.

The performance of the analytical methods used in the clinical studies was sufficiently summarised. Precision and accuracy values for method performance characteristics remained in pre-determined validation range (within 15% of nominal value, except 20% at the LLQ) and are thus acceptable.

Different QCs were used in the different studies, during the validation of bioanalytical methods TM.1296 and MW1477, a medium QC used for vericiguat was around 5%, and high QC was around 80% of the calibration curve; thus, middle parts, i.e. 5 - 80 % (for M-1 from 10 - 80%) of the calibration curves were not covered at all. That kind of selection of the QC levels does not comply with the EMA bioanalytical method validation guideline. However, as the different methods have been appropriately cross-validated, this deviation can be accepted.

The pharmacokinetics in healthy volunteers have been extensively characterised. The applicant evaluated the pharmacokinetics in the target HFrEF patient population using population PK modelling. Phase 2-3 population PK model and Phase 1-2-3 model are considered most relevant for the current application. The submitted goodness of fit plots show that the model performance of both PK models is reasonably well. In the phase 1-2-3 model, some unexplained differences between healthy volunteers and heart failure patients remain, despite that model includes an additive shift in Log VC for heart failure subjects. Possibly this may be caused by differences in disease severity, but this cannot be verified with available data.

The one-compartment Phase, 2-3 model, contains sparse sampling data of heart failure patients. The two-compartment Phase 1-2-3 model contains the same Phase 2-3 data but also dense sampling, healthy volunteer data. Differences in sampling schemes mainly cause the different disposition models. The final parameter estimates of both PK models were comparable. In the Phase 1/2/3 PopPK two-compartment model, the estimated sum of central volume of distribution (Vc) and peripheral volume of distribution (Vp) was 40,4 L and the Phase 2/3 one-compartment PopPK model, the estimate of the volume of distribution was 46.8 L. Overall clearance was in a similar range and results of covariate analysis were consistent between the two population studies.

In the phase 1/2/3 PopPK model, health status was identified as a relevant covariate on the volume of distribution (Vc/F). The steady-state exposure is estimated to be about 20% higher in HF patient when compared to healthy volunteers based on model simulations. This difference could be due to

congestion in HF patients and other factors being different in healthy volunteer versus HF patient populations and corresponding clinical studies.

The submitted Population PK data support the translation of the phase I program data to the patient population. No dense sampling studies in heart failure patients are needed.

In healthy volunteers, dose-proportional pharmacokinetics was observed, but in heart failure patients, vericiguat exhibited slightly less than dose-proportional pharmacokinetics. The differences may be caused by the differences in administration conditions between the strictly controlled phase 1 study conditions and administration in the ambulant situation.

The bioavailability of vericiguat increases by approximately 40% when taken with food and administration with food reduces the variability. It is supported to recommend intake with food.

Special populations

Vericiguat is extensively metabolised in the liver and kidneys by glucuronidation via UGT1A1 and UGT1A9. Therefore, the applicant evaluated the effects of renal and hepatic impairment.

Population PK data in HF patients with renal impairment has been used as a basis for dosing recommendations in this subpopulation. Further a (dense sampling) study 15813, P009 in subjects with renal impairment has been conducted. In the Population PK study, the impact of renal impairment was lower, in patients with heart failure with moderate and severe renal impairment, the mean exposure (AUC) of vericiguat was increased by 13% and 20%, respectively, compared to patients with normal renal function. In study 15813, P009 up to 2-fold increases of vericiguat exposure was observed patients with moderate and severe renal impairment. In section 5.2 of the SmPC the data of both studies have been provided, including an explanation that differences may be attributed to differences in study design and size. In principle, it is agreed to use the HF population PK data (with data from the Victoria phase III study and the phase II studies) as a basis for dosing recommendations for patients with renal impairment, as this is considered the most relevant population for vericiguat. However, the comparison of population PK data and the results of the renal impairment study is difficult. Because it is not clear from the pop PK model, if subjects with renal impairment achieved the same 10mg target dose as has been administered in HF patients with normal renal function. In the placebo-controlled Victoria phase III study patients with mild, moderate and severe renal impairment, the majority received the target dose of 10 mg. Of the subjects with mild renal impairment 83% received the target dose, 80% of the subjects with moderate renal impairment and 75% of the subjects with severe renal impairment, regardless of treatment. Based on these results, renal impairment does not have a clinically relevant impact on the dose administered. Furthermore, vericiguat is titrated based on efficacy and safety.

In subjects with mild hepatic impairment (Child-Pugh A) the mean exposure (AUC) to vericiguat was 21% higher compared to healthy subjects with normal hepatic function and in subjects with moderate hepatic impairment (Child-Pugh B), mean exposure to vericiguat was approximately 47% higher compared to their healthy subjects with normal hepatic function. These elevations are not considered clinically relevant as the effect of mild and moderate hepatic impairment was within normal subject variability or only slightly above. Further, it should be considered that vericiguat dose is only up-titrated when tolerated by the patient. Vericiguat has not been studied in patients with severe hepatic impairment (Child-Pugh C) and is not recommended in these patients. This is agreed upon. due to the lack of study data but also because glucuronidation may be affected in patients with severe hepatic impairment.

Both metabolic enzymes UGT1A1 and UGT1A9 have known polymorphisms affecting the activity leading to a decrease (e.g. UGT1A1*6, and UGT1A1*28) or an increase (e.g. UGT1A1*36). The

potential impact of UGT1- polymorphism has not been investigated, but the impact is expected to be low because vericiguat is titrated based on the efficacy and safety. No further studies are warranted.

Interactions

The vericiguat potential for interactions has been extensively investigated *in vitro*, in clinical drug-drug interaction studies and using PBPK modelling.

Vericiguat as victim

As can be expected of a drug that is mainly metabolised by UGT1A1 and 1A9 inhibitors of UGT1A1 and 1A9 affected the metabolism of vericiguat to M-1 *in vitro*. Based on *in vitro* tests, metabolism via UGT1A9 is predicted to be the main metabolic route, and the contribution of UGT1A1 is predicted to be less relevant (the [I]max,u/IC50 ratio were 0.307 and 0.536 for the UGT1A9 inhibitors mefenamic acid and niflumic acid, respectively and <0.011 for UGT1A1 inhibitor atazanavir). However, in the clinical DDI study 17116, a non-relevant 20% increase of the vericiguat exposure was observed upon coadministration with mefenamic acid. The mild effect of mefenamic acid on vericiguat exposure may be caused because mefenamic acid is not a strong enough inhibitor of UGT1A9 or by the significant contribution of UGT1A1 to the vericiguat metabolism (one UGT may be able to take over the metabolism when the other UGT is inhibited). The Applicant did not conduct a clinical DDI study with a general UGT inhibitor to assess the maximum impact of UGT inhibition. Because no acknowledged strong inhibitors of UGT1A1 and 1A9 or a general strong inhibitor of both UGTs are available this is considered acceptable. The applicant committed to monitor potentially relevant PK DDIs during the regular PSUR procedure and/or to re-evaluate the PK of vericiguat once an acknowledged a general strong UGT inhibitor is available. This approach is considered acceptable. A warning was included in section 4.5 of the SmPC regarding concomitant administration with UGT1A1 and/or 1A9 inhibitors. As strong inhibition of UGT1A9 or combined UGT1A9/1A1 has not been tested in clinical drug-drug interaction studies due to the lack of available inhibitors, the clinical consequences of co-administration with these medicinal products are currently unknown.

In clinical studies the strong CYP3A inhibitor (ketoconazole) and a strong inducer (rifampicin) did not have a significant effect on the PK of vericiguat.

Co-treatment with medicinal products that increase gastric pH, such as proton pump inhibitors, decreased the exposure of vericiguat (~50% reduction in Cmax and ~30% reduction in AUC). As vericiguat is intended for chronic use, the effect on AUC is considered most relevant. The observed mild decrease of the exposure is not considered clinically relevant. Furthermore, these studies were performed under fasted conditions, and vericiguat is recommended to be taken under fed conditions, in which case the gastric pH is higher.

PBPK modelling was performed to explore the effects of DDI potential with atazanavir (UGT1A1-mediated DDI) and mefenamic acid (UGT1A9-mediated DDI). Currently, PBPK models cannot be used for UGT DDIs and to waive clinical DDI studies. Furthermore, based on the main biotransformation pathway, the lack of information on the effect of genetic polymorphisms in UGT, and uncertainties regarding mefenamic acid as an inhibitor of UGT1A9 in the clinical DDI studies, it cannot be concluded that UGT inhibition by concomitant medicinal products will not affect the PK of vericiguat. Therefore, these PBPK modelling simulations have not been included in the SmPC.

Vericiguat as perpetrator

Many in vitro studies were performed to assess the inhibitory potential of vericiguat, were performed. Vericiguat was an inhibitor of UGT1A9 at maximal intestinal concentrations with an IC50 value of 10.6 µM. Vericiguat was not an inhibitor of the other UGTs investigated and did also not affect any of the

investigated CYP enzymes or transporters. In clinical DDI studies, no effects were observed of vericiguat on the PK of a substrate of CYP3A (midazolam) and a substrate of CYP2C9 (S-warfarin), which is in line with the in vitro study results. The potential intestinal inhibition of UGT1A9 by vericiguat was not investigated because the expression of UGT1A9 in the intestine is very limited and most likely not sufficient to cause high first-pass metabolism via UGT1A9 in the intestine.

Pharmacodynamics

Vericiguat is a stimulator of soluble guanylate cyclase (sGC). Heart failure is associated with impaired synthesis of nitric oxide (NO) and decreased activity of its receptor, sGC. Vericiguat restores the relative deficiency in this signalling NO-sGC-cGMP pathway by directly stimulating sGC, independently of and synergistically with NO, to augment intracellular cGMP levels, which may improve both myocardial and vascular function. The mechanism of action of a sGC stimulator, i.e. relaxation of the smooth muscles in the vasculature leading to changes in haemodynamics, is supported by clinical data.

The PD effects of vericiguat were evaluated after single and multiple-dose administrations in healthy subjects (Study 15355 and Study 15357, respectively). A single dose of vericiguat resulted in a significant decrease in systemic vascular resistance, increase in cardiac output, and cardiac index (at the dose of 7.5 mg and higher) and a significant increase in heart rate (at the dose of 5.0 mg and higher)(Study 15355). Multiple doses of 1.25 mg, 5mg, 10 mg qd or 5 mg bid of vericiguat resulted in significant decreases in systemic vascular resistance, increase in cardiac output and cardiac index and increase in heart rate, which were not dose-dependent (Study 15357). The increase in heart rate is a compensatory reaction to the blood pressure-lowering effect of vericiguat through the baroreflex, which may have led to no effect on systolic and diastolic blood pressure after multiple-dose of vericiguat. Further, treatment with vericiguat resulted in significant increases in aldosterone (at a single doses of 5.0 mg and higher) and plasma renin activity (at a single dose of 5.0 mg and higher), indicating the extent of compensation to the vasodilative effect.

Any QT-prolonging or other arrhythmic potential for vericiguat is unlikely based on the absence of any pro-arrhythmic effect in in vitro, preclinical, dedicated QT study in CAD subjects and phase 3 ECG data.

In DDI studies, no clinically relevant PD interactions were observed when vericiguat was co-administered with acetylsalicylic acid (Study 15838), warfarin (Study 15839), or sacubitril/valsartan (Study 17745). Further, the provided clinical DDI studies on co-administration of vericiguat with nitrates (Study 17115, 17849, and 18582) do not provide sufficient evidence to rule out any clinically relevant PD interaction. However, in VICTORIA, 269 subjects (10.8%) in the vericiguat group used nitrate at one or more visits, of which 67 subjects (2.7%) used long-acting nitrates or NO donors. These data showed no adverse events of symptomatic hypotension or syncope when vericiguat was co-administered with any nitrate use, including long-acting nitrates or NO donors, although these data was very limited (n=67). Due to the limited experience when vericiguat and long-acting nitrates are used concomitantly in patients with heart failure, a warning to consider the potential for symptomatic hypotension in case of concomitant treatment is stated in the SmPC. Based on the DDI with sildenafil (Study 17743), a recommendation not the use of vericiguat in combination with PDE-5 inhibitor is stated in the SmPC.

PK/PD models using data from SOCRATES-REDUCED (Study 17401) and VICTORIA (Study 20965) showed that vericiguat exposure was correlated with decreases in SBP after the first dose; however, the change in SBP from baseline during the remaining days of the titration period was not associated with vericiguat exposure, indicating adaptation to vericiguat treatment. Furthermore, an exposure-dependent reduction of NT-proBNP by vericiguat was observed, dependent on baseline NT-proBNP; greater exposure-dependent reduction in NT-proBNP in the lowest NT-proBNP quartiles.

Exposure-PD effect analyses across different phase 1 studies in healthy volunteers (Study 15356, Study 15357, Study 15836) demonstrated greater increases in cardiac index and cardiac output and greater decreases in systemic vascular resistance at higher plasma concentrations. In contrast, no clear effect concerning HR was observed.

2.4.5. Conclusions on clinical pharmacology

Generally, the pharmacokinetics and pharmacodynamics of vericiguat have been sufficiently characterised.

2.5. Clinical efficacy

This application is based on efficacy data obtained from the following studies:

- Phase II dose-finding study: SOCRATES-REDUCED (Study 15371)
- Phase III study: VICTORIA (Study 16493)

An overview of the Phase II and Phase III clinical development program is provided in **Table 1**.

2.5.1. Dose response study

In the randomized parallel-group, placebo-controlled, double-blind, multicentre 12-week dose-finding study (SOCRATES-REDUCED), 4 vericiguat dose regiments (1.25 mg, 2.5 mg, 2.5 up-titrated to 5 mg, and 2.5 up-titrated to 10 mg) relative to placebo were evaluated in patients with worsening HFrEF. Titration of the dose was dependent on the subject's tolerance determined by SBP. At 12 weeks, the primary efficacy endpoint, change from baseline in log-transformed NT-proBNP, was not significantly different between the pooled vericiguat group and placebo. However, the secondary analysis showed a dose-response relationship in the reduction of NT-proBNP after 12 weeks in the vericiguat group. The starting dose of 2.5 mg vericiguat titrated at 2-week intervals to a target dose of 10 mg resulted in the greatest reduction in NT-proBNP at 12 weeks compared with placebo (p=0.0483) (**Table18**).
Concerning safety, adverse events leading to discontinuation were reported in 42 of the 455 subjects (9.2%); the incidence did not increase with increasing dosages of vericiguat. The overall incidence of drug-related hypotension was 4.0% (18 subjects) and was notably highest in the 2.5-10 mg group (8 subjects; 8.8%) compared with the lower-dose vericiguat and placebo groups, where the incidence ranged from 2.2% in each of the three lower vericiguat dosage groups and 4.3% in the placebo group.

Table 18. Comparison of the Primary Efficacy Variable Change in Log transformed NT-proBNP From Baseline to Week 12 (Visit 5)

Treatment Comparison	Difference of Means vs Placebo - log scale	90% CI of Difference	Ratio of Geometric Means vs Placebo -Back Transformed	90% CI of Ratio	t-test *p*-value (one-sided)
Vericiguat Pool	-0.1220	-0.32 to 0.07	0.885	0.73 to 1.08	0.1506
Vericiguat 1.25 mg	0.0151	-0.21 to 0.24	1.015	0.81 to 1.27	0.5444
Vericiguat 2.5 mg	-0.0396	-0.26 to 0.18	0.961	0.77 to 1.20	0.3841
Vericiguat 2.5 to 5 mg	-0.0731	-0.31 to 0.16	0.930	0.73 to 1.18	0.3402
Vericiguat 2.5 to 10 mg	-0.2494	-0.50 to -0.00	0.779	0.61 to 1.00	0.0483

The 3 highest vericiguat dose groups (2.5 mg, 2.5 to 5 mg, 2.5 to 10 mg) were included in the pool.
Mean and SD are on the log scale (log [pg/mL]).
Geometric mean and SD are on the original scale (pg/mL).
Since the primary analysis was not significant, all *p*-values are only descriptive.
CI=confidence interval; NT-proBNP=N-terminal pro-brain natriuretic peptide.

2.5.2. Main study

As noted previously, Study 16493 (VICTORIA) is the phase III pivotal study to support the proposed indication.

Title of study

Study 16493- A Randomized Parallel-Group, Placebo-Controlled, Double-Blind, Event-Driven, Multi-Center Pivotal Phase III Clinical Outcome Trial of Efficacy and Safety of the Oral sGC Stimulator Vericiguat in Subjects With Heart Failure With Reduced Ejection Fraction (HFrEF) - VerICiguaT GlObal Study in Subjects With Heart Failure With Reduced EjectIon FrAction (VICTORIA).

Methods

Study Participants

The main inclusion/exclusion criteria are provided in **Table19** below.

Table 19. Key inclusion/exclusion criteria of the VICTORIA study

Study 16493
Inclusion Criteria
- Be male or female, aged ≥18 years.
- Have a history of chronic HF (NYHA class II to IV) on standard therapy before qualifying HF decompensation
- Have a previous HF hospitalization within 6 months prior to randomization or IV diuretic treatment for HF (without hospitalization) within 3 months prior to randomization.
- Have BNP or NT-proBNP levels within 30 days prior to randomization as follows: • NT-proBNP ≥1000 pg/mL or BNP ≥300 pg/mL in sinus rhythm • NT-proBNP ≥1600 pg/mL or BNP ≥500 pg/mL in atrial fibrillation
- Have a LVEF <45% assessed within 12 months prior to randomization.
- Meet one of the following criteria: a. Male

b. Confirmed postmenopausal women or women without childbearing potential based on surgical treatment (such as bilateral tubal ligation, bilateral oophorectomy, bilateral salpingectomy, or hysterectomy) or a congenital or acquired condition that prevents childbearing c. Women of reproductive potential who agree to avoid becoming pregnant through abstinence from heterosexual activity or use (or have partner use) acceptable contraception during heterosexual activity
Exclusion Criteria
- Was clinically unstable at the time of randomization as defined by: a. Administration of any IV treatment within 24 hours prior to randomization, and/or b. Systolic blood pressure <100 mm Hg or symptomatic hypotension.
- Had concurrent or anticipated use of long-acting nitrates or nitric oxide donors including isosorbide dinitrate, isosorbide 5-mononitrate, pentaerythritol tetranitrate, nicorandil or transdermal nitroglycerin patch, and molsidomine
- Had concurrent use or anticipated use of PDE5 inhibitors such as vardenafil, tadalafil, and sildenafil
- Had concurrent use or anticipated use of a sGC stimulator such as riociguat
- Had known allergy or sensitivity to any sGC stimulator
- Was awaiting heart transplantation (United Network for Organ Sharing Class 1A/1B or equivalent), receiving continuous IV infusion of an inotrope, or has/anticipates receiving an implanted ventricular assist device
Cardiac comorbidity
- Had primary valvular heart disease requiring surgery or intervention, or was within 3 months after valvular surgery or intervention
- Had hypertrophic obstructive cardiomyopathy
- Had acute myocarditis, amyloidosis, sarcoidosis, or Takotsubo cardiomyopathy
- Had post-heart transplant cardiomyopathy
- Had tachycardia-induced cardiomyopathy and/or uncontrolled tachyarrhythmia
- Had acute coronary syndrome including unstable angina, NSTEMI or STEMI, or coronary revascularization (CABG or PCI) within 60 days prior to randomization, or indication for coronary revascularization at time of randomization
- Had symptomatic carotid stenosis, TIA, or stroke within 60 days prior to randomization
- Had complex congenital heart disease
- Had active endocarditis or constrictive pericarditis
Noncardiac comorbidity
- Had an eGFR <15 mL/min/1.73 m2 or chronic dialysis
- Had severe hepatic insufficiency such as with hepatic encephalopathy
- Had malignancy or other noncardiac condition limiting life expectancy to <3 years
- Required continuous home oxygen for severe pulmonary disease
- Had current alcohol and/or drug abuse
- Had previous (≤30 days of randomization) or concomitant participation in another interventional clinical study with investigational product(s).
- Had a mental or legal incapacitation and was unable to provide informed consent
- Had a medical disorder, condition, or history thereof that in the opinion of the investigator would impair the subject's ability to participate or complete the study
- Had an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who was investigational site or Sponsor staff directly involved with this trial
- Had Interstitial Lung Disease
- Was pregnant or breastfeeding or planned to become pregnant or to breastfeed during the trial

Treatments

The design of the study included a screening period of up to 30 days, a randomized double-blind treatment period (event-driven study duration), in which eligible patients started with 2.5 mg vericiguat or matching placebo followed by 2 dose doublings in 2-week intervals to reach the 10 mg dose, dependent on the subject's tolerance determined by SBP and symptoms of hypotension (**Table 20**), and a follow-up period in which each subject will be followed for 14 days after the last treatment dose.

Furthermore, all subjects were to receive standard of care HF treatment following locally relevant guidelines such as ACC/AHA and ESC Guidelines for the Management of Heart Failure recommendations at the discretion of the treating investigator based on the individual subject's

tolerability. Investigators were to provide a rationale for all subjects who were not receiving standard of care HF treatment at the time of randomization.

Table 80. Systolic blood pressure 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 on 10 mg target dose **or** • SBP between 90 and <100 mm Hg	Maintain Dose
SBP <90 mm Hg, asymptomatic	• If currently on 5 or 10 mg decrease dose • If currently on 2.5 mg interrupt dose
SBP <90 mm Hg, symptomatic	Interrupt Dose

Objectives

The objectives/endpoint of the study are presented in **Table 211**.

Table 9. Objectives and endpoints of VICTORIA

Primary Objective	Primary Endpoint
To evaluate the efficacy of the oral sGC stimulator vericiguat in comparison to placebo on a background of standard of care in increasing the time to first occurrence of the composite of CV death or HF hospitalization in subjects with HFrEF.	CV death or HF hospitalizations
Secondary Objectives	**Secondary Endpoints**
To evaluate the efficacy of vericiguat in increasing the time to CV death in comparison to placebo.	CV death
To evaluate the efficacy of vericiguat in increasing the time to first HF hospitalization in comparison to placebo.	HF hospitalization
To evaluate the efficacy of vericiguat in increasing the time to total HF hospitalizations (first and recurrent) in comparison to placebo.	Total HF hospitalizations (first and recurrent)
To evaluate the efficacy of vericiguat in increasing the time to the first occurrence of the composite of all-cause mortality or HF hospitalization in comparison to placebo.	All-cause mortality or HF hospitalization
To evaluate the efficacy of vericiguat in increasing the time to all-cause mortality in comparison to placebo.	All-cause mortality
To evaluate the safety and tolerability of vericiguat.	Adverse events (AEs)

An independent CEC performed a blinded adjudication of potential endpoint events. Per the CEC Charter, a death whose cause was undetermined was considered to be a CV death. The study

continued until the protocol-required number of CV deaths was observed. All subjects were followed through their final study contact to assess potential efficacy and safety events.

Outcomes/endpoints

Sample size

Randomisation and Blinding (masking)

Randomization occurred centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). Subjects were assigned randomly in a 1:1 ratio to vericiguat or matching placebo. Treatment allocation/randomization was stratified by region (Eastern Europe, Western Europe, North America, Latin and South America and the Asia Pacific) and race (Black Non-black). The stratification variable race was nested within the region North America, because of specific class I treatment recommendations for black race in the ACC/AHA guideline.

A double-blinding technique with in-house blinding was used. Vericiguat and matching placebo were packaged identically. The subject, the investigator and Sponsor personnel or delegate(s) involved in the treatment or clinical evaluation of the subjects were unaware of the group assignments.

Statistical methods

The sample size estimation was based on a 1:1 randomization and a study-wise one-sided significance level of 0.025. In accordance with the initial planned interim analysis in the protocol, the nominal one-sided significance level was planned to be 0.0241 at the final analysis. A conservative approach of power calculation based only on the final analysis was used.

The study was event-driven. It was planned to accrue subjects for 30 months and have a follow-up of 9 months after the last subject is included in the study. It was assumed that 2% of subjects per year will prematurely stop study medication and either object to further follow-up or be lost to follow-up, despite efforts to contact them. In addition, was assumed that approximately 10% per year of subjects will stop study treatment and can be followed up off treatment for the primary endpoint. When a subject stopped treatment prematurely, it was assumed that the hazard for CV death and HF hospitalization would have the hazard of the placebo group afterwards.

The sample size calculation was driven by the CV death component of the composite primary endpoint. For the CV death component, the expected event rate in the comparator group after 12 months was 11%. The relative risk reduction with vericiguat was assumed to be 20%, relating to an HR of 0.8. Using the log-rank test, a sample size of 4872 subjects and a total of 782 CEC confirmed CV deaths was required to achieve 80% power. For the comparator arm, the event rate of the composite endpoint, i.e. first HF hospitalization or CV death, was expected to be 23% after 12 months. The relative risk reduction with vericiguat was assumed to be 20%, relating to an HR of 0.8. With a sample size of 4872 subjects, it was expected to observe 1561 subjects with a composite endpoint event and expected power of approximately 98%.

The analysis population for the primary and secondary efficacy endpoint analyses used the Intention-to-Treat (ITT) population. The ITT population included all randomized subjects. The subjects were analyzed according to the planned treatment. The All-Subjects-as-Treated (ASaT) population were

used for safety analyses. The ASaT population included all subjects who have taken at least one dose of study drug and were analyzed according to the actual treatment received.

The analysis of the primary endpoint was based on results from adjudication and tested if the time to the first occurrence of the composite endpoint was prolonged in the vericiguat treatment group. Randomized subjects without any HF hospitalization or CV death event at the time of analysis were censored at their last available information or the date of their non-CV death. The analysis was performed with a one-sided log-rank test, stratified by the strata used in randomization.

The overall study-wise one-sided type I error rate was controlled at 0.025. If the z-value from the one-sided stratified log-rank test was larger than the critical quantile from the standard normal distribution ($z_{1-\alpha}$), the null hypothesis was rejected in favour of the alternative hypothesis.

Kaplan-Meier estimates of the primary composite endpoint (95% confidence interval) survival curves were presented for each treatment group. Hazard ratio, relative risk reduction and corresponding 95% confidence intervals were estimated based on a Cox proportional hazards model stratified by the same factors as used for the primary efficacy analysis.

A one-sided stratified log-rank test similar to the one used for the primary efficacy endpoint were used for the secondary time to endpoint analyses. The primary approach for time-to total HF hospitalization analysis used the Andersen-Gill model to compare the vericiguat treatment group to placebo, including the stratification factors used for randomization as fixed effects. Robust standard errors were used to account for correlations of event times within a subject. The superiority of vericiguat over placebo in prolonging the time to total HF hospitalization were concluded if the upper limit of the confidence interval of the hazard ratio was below 1. Estimates of treatment comparisons and effect size, including 95% confidence intervals, were provided based on the fitted model. In addition, time to total HF hospitalizations and CV death were analyzed using the Wei, Lin, Weissfeld (WLW) method.

Subjects who prematurely withdrew from study treatment were followed for further data collection. As long as the subject did not withdraw consent for any further data collection, every effort was made to collect at least data on the components of the primary endpoint.

Sensitivity analyses were performed to assess the impact of potential informative censoring and missing data using simulation approaches in several scenarios: missing at random and missing not at random (reference-based approach, delta adjustment approach and tipping point analyses).

In addition to the intention-to-treat analysis (ITT) approach as described above, on-treatment analyses were performed on the primary composite endpoint, secondary composite endpoints, and exploratory endpoints.

The multiplicity adjustment approach for the secondary endpoints were separated into two families. The first family consisted of the components of the primary endpoint, time to CV death and time to first HF hospitalization, and were tested alongside the primary endpoint without multiplicity adjustment. The second family consisted of the endpoints of time to total HF hospitalization, time to all-cause mortality, and time to the first occurrence of the composite of HF hospitalization or all-cause mortality and were tested hierarchically.

The protocol described a potential interim analysis for assessing efficacy and futility. Enrolment time was shorter than initially planned and the cardiovascular death event rate was higher than initially assumed. The interim analysis was planned at 10 months median safety follow up; following this plan, the interim decision would not be made until after the study close-out had already started. Therefore, a decision was made not to perform the interim analysis. Accordingly, no multiplicity adjustment for interim analysis was applied, and a one-sided alpha level of 0.025 was used for all hypothesis testing at the final analysis.

Results

Participant flow

Eligible subjects were male and female subjects aged 18 years or older with chronic HF with reduced ejection fraction (<45%), elevated levels of natriuretic peptides, previous HF decompensation (defined as HF hospitalization within 6 months prior to randomization or use of IV diuretics for HF [without hospitalization] within 3 months prior to randomization) (**Table 22**). Additionally, all subjects were required to be clinically stable (defined as SBP ≥100 mm Hg and no administration of IV therapy) at the time of randomization.

Table 10. Disposition of subjects- ITT population

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Not Randomized					1,807	
Subjects in population	2,526		2,524		5,050	
Gender (Age Range in Years)						
Male	1,921	(24 to 94)	1,921	(23 to 97)	3,842	(23 to 97)
Female	605	(26 to 98)	603	(24 to 94)	1,208	(24 to 98)
Status in Trial						
Completed	1,952	(77.3)	1,937	(76.7)	3,889	(77.0)
Discontinued	574	(22.7)	587	(23.3)	1,161	(23.0)
Death	541	(21.4)	552	(21.9)	1,093	(21.6)
Lost To Follow-Up	14	(0.6)	14	(0.6)	28	(0.6)
Site Terminated By Sponsor	4	(0.2)	3	(0.1)	7	(0.1)
Withdrawal By Subject	15	(0.6)	18	(0.7)	33	(0.7)
Status for Study Medication in Trial						
Started	2,519		2,515		5,034	
Completed	1,547	(61.4)	1,561	(62.1)	3,108	(61.7)
Discontinued	972	(38.6)	954	(37.9)	1,926	(38.3)
Adverse Event	177	(7.0)	160	(6.4)	337	(6.7)
Death	358	(14.2)	386	(15.3)	744	(14.8)
Lost To Follow-Up	9	(0.4)	11	(0.4)	20	(0.4)
Non-Compliance With Study Drug	49	(1.9)	49	(1.9)	98	(1.9)
Physician Decision	176	(7.0)	156	(6.2)	332	(6.6)
Protocol Deviation	8	(0.3)	2	(0.1)	10	(0.2)
Withdrawal By Subject	195	(7.7)	190	(7.6)	385	(7.6)

Study intervention exposure, titration, and dose modification

As of the primary completion date of the study (18 JUN 2019), the mean duration of exposure to any dose of vericiguat was 375.5 days (max 964 days) and to 10 mg vericiguat was 362 days (max 935 days). The mean duration of exposure to placebo was 374.7 days (max 966 days). The mean average dose of study intervention was 7.8 mg in the vericiguat group and 8.0 mg (placebo equivalent) in the placebo group. Of the 5034 subjects treated, the proportion of subjects titrated to the 10-mg target dose at some point in the study was similar between treatment groups (81.9% in the vericiguat group and 84.1% in the placebo group). The proportion of subjects who attained 10 mg vericiguat or matching placebo over the course of the study was 73.9% during Weeks 4 to 8, 81.1% during Weeks 9 to 16, 86.4% during Weeks 17 to 32, 90.3% during Weeks 49 to 64, and 92.3% during Weeks 97 to 112. The proportion of subjects on the 10 mg vericiguat dose (or placebo equivalent) was approximately 1% to 3% higher in the placebo group than in the vericiguat group throughout the study. The proportion of subjects who reached the 10-mg dose (vericiguat or matching placebo) by

Day 56 and stayed on the 10-mg dose for at least 80% of the treatment period was similar in both groups (61.6% in the vericiguat group and 63.8% in the placebo group).

Of the 4913 subjects with study medication dose modification data, the proportion of subjects who required a dose decrease at 1 or more visits (8.9% and 7.4% in the vericiguat and placebo group, respectively) or a dose interruption (17.0% versus 16.4%) was similar between treatment groups.

Recruitment

Conduct of the study

Protocol deviations

Important protocol deviations were reported for 898 subjects in this study. Of these, 133 subjects had important protocol deviations that were considered to be clinically important (**Table 23**). The proportion of subjects with clinically important protocol deviations, overall and by category, was similar in the vericiguat and placebo groups.

Table 11. Clinically Important Protocol Deviation Summary

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	2,526		2,524		5,050	
With one or more clinically important protocol deviations	65	(2.6)	68	(2.7)	133	(2.6)
With no clinically important protocol deviations	2,461	(97.4)	2,456	(97.3)	4,917	(97.4)
Inclusion/ Exclusion Criteria	**9**	**(0.4)**	**9**	**(0.4)**	**18**	**(0.4)**
Exclusion 01 (subject clinically stable per entry requirements) not met and participant entered the trial.	4	(0.2)	2	(0.1)	6	(0.1)
Exclusion 03 (concomitant use of phosphodiesterase type 5 inhibitors) met and participant entered the trial.	1	(0.0)	1	(0.0)	2	(0.0)
Exclusion 20 (current alcohol and/or drug abuse) met and participant entered the trial.	1	(0.0)	1	(0.0)	2	(0.0)
Exclusion 23 (unable to participate or complete the study) met and participant entered the trial.	0	(0.0)	1	(0.0)	1	(0.0)
Exclusion 25 (interstitial lung disease) met and participant entered the trial.	2	(0.1)	1	(0.0)	3	(0.1)
Inclusion 05 (brain natriuretic peptide or NT-proBNP required entry levels) not met and participant entered the trial.	1	(0.0)	2	(0.1)	3	(0.1)
Inclusion 06 (left ventricular ejection fraction of < 45% within 12 months of randomization) not met and participant entered the trial.	0	(0.0)	1	(0.0)	1	(0.0)
Informed Consent Form	**0**	**(0.0)**	**3**	**(0.1)**	**3**	**(0.1)**
Participants with no documented initial consent to enter the trial.	0	(0.0)	3	(0.1)	3	(0.1)
Prohibited Medications	**2**	**(0.1)**	**6**	**(0.2)**	**8**	**(0.2)**
PDE5 inhibitors co-administered with study drug.	2	(0.1)	6	(0.2)	8	(0.2)
Safety Reporting	**29**	**(1.1)**	**26**	**(1.0)**	**55**	**(1.1)**
Participants with reportable Safety Events and/or follow up Safety Event information that were not reported per the timelines outlined in the protocol.	29	(1.1)	26	(1.0)	55	(1.1)
Study Intervention	**24**	**(1.0)**	**24**	**(1.0)**	**48**	**(1.0)**
Participants who received incorrect study treatment and/or were administered improperly stored study treatment.	11	(0.4)	21	(0.8)	32	(0.6)
Study treatment was NOT interrupted at study visit in which subject's mean SBP <90 mm Hg and symptomatic.	3	(0.1)	2	(0.1)	5	(0.1)
Subject received an overdose of study medication (per protocol definition) that was associated with an adverse effect.	7	(0.3)	0	(0.0)	7	(0.1)
Subjects with an interruption >5 days with an interruption due to intolerability and did not restart study treatment at 2.5 mg dose according to protocol resumption guidance.	3	(0.1)	1	(0.0)	4	(0.1)
Trial Procedures	**6**	**(0.2)**	**5**	**(0.2)**	**11**	**(0.2)**
Subject was accidently assigned a randomization number in error.	6	(0.2)	5	(0.2)	11	(0.2)

Every subject is counted a single time for each applicable row and column.
Subjects may report multiple protocol deviations in one or more categories.
Based on data up to the primary completion date (18Jun2019).

Source: [P001MK1242: adam-adsl] [P001MK1242: sdtm-dv; suppdv]

GCP compliance issues

One site was closed during the study due to GCP non-compliance, including identified falsification of study eligibility data for 3 of 8 randomized subjects at the site (Inclusion Criterion No. 5: NT-

proBNP/BNP values for 3 subjects and Inclusion Criterion No. 6: LVEF <45% assessed within 12 months for 1 subject), falsification of principal investigator signature/initials, and missing or incomplete source data not in compliance with ALCOA standards. Subjects were offered the option to transfer to another site for continued study follow-up, but all declined. After trial site closure, the Sponsor entered into a separate clinical trial research agreement with the site that included ongoing source document retainment and data reporting for potential endpoint events and vital status available after site closing. The data generated for the 8 subjects randomized at this site were included in all study analyses because the primary analysis was based on the ITT population that included all randomized subjects.

Baseline data

The treatment groups were comparably balanced for all baseline demographics (**Table 244** and **Table 25**). A majority of subjects were male, and more than 60% were of the white race. The mean age of the subjects was 67.3 years, and 1568 subjects (31%) were ≥75 years old at baseline. Approximately half of subjects were from the European strata, one-quarter were from Asia Pacific, and one-quarter were from the Americas. Israel and South Africa were prespecified to be included in the Eastern European stratum.

Approximately two-thirds of the subjects in VICTORIA enrolled within 3 months of an HF hospitalization; the remaining subjects were approximately equally distributed between those enrolled within 3 to 6 months of HF hospitalization and those enrolled within 3 months of outpatient treatment with IV diuretics for worsening HF. The median time from the index event to randomization was 32.0 days. The mean time from initial HFrEF diagnosis to randomization was 4.8 years.

Approximately half of all subjects had an EF <30%, and 14.3% of patients had an EF ≥40% and ≤45%. At randomization, a majority of subjects were categorized as either NYHA Class II (58.9%) or III (39.7%) and the median NT-proBNP level was 2816.0 pg/mL. The mean eGFR at randomization was 61.5 mL/min/1.73 m2. Overall, 10.0% of randomized subjects had an eGFR ≤30 mL/min/1.73 m^2.

Table 12. Subject Demographics

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	2,526		2,524		5,050	
Gender						
Male	1,921	(76.0)	1,921	(76.1)	3,842	(76.1)
Female	605	(24.0)	603	(23.9)	1,208	(23.9)
Age (Years)						
≤50	223	(8.8)	247	(9.8)	470	(9.3)
51 to 60	446	(17.7)	427	(16.9)	873	(17.3)
61 to 70	758	(30.0)	753	(29.8)	1,511	(29.9)
71 to 80	737	(29.2)	778	(30.8)	1,515	(30.0)
≥81	362	(14.3)	319	(12.6)	681	(13.5)
Mean	67.5		67.2		67.3	
SD	12.2		12.2		12.2	
Median	69.0		68.0		69.0	
Range	24 to 98		23 to 97		23 to 98	
Race						
American Indian Or Alaska Native	24	(1.0)	28	(1.1)	52	(1.0)
Asian	571	(22.6)	561	(22.2)	1,132	(22.4)
Black	123	(4.9)	126	(5.0)	249	(4.9)
Multi-Racial	183	(7.2)	180	(7.1)	363	(7.2)
Native Hawaiian Or Other Pacific Islander	3	(0.1)	11	(0.4)	14	(0.3)

Not Reported	1	(0.0)	0	(0.0)	1	(0.0)
White	1,621	(64.2)	1,618	(64.1)	3,239	(64.1)
Ethnicity						
Hispanic Or Latino	410	(16.2)	403	(16.0)	813	(16.1)
Not Hispanic Or Latino	2,044	(80.9)	2,065	(81.8)	4,109	(81.4)
Not Reported	39	(1.5)	29	(1.1)	68	(1.3)
Unknown	33	(1.3)	27	(1.1)	60	(1.2)
Geographic Region						
Eastern Europe	848	(33.6)	846	(33.5)	1,694	(33.5)
Western Europe	443	(17.5)	446	(17.7)	889	(17.6)
Asia Pacific	592	(23.4)	591	(23.4)	1,183	(23.4)
Latin and South America	362	(14.3)	362	(14.3)	724	(14.3)
North America	281	(11.1)	279	(11.1)	560	(11.1)
Race in North America						
Black	62	(2.5)	61	(2.4)	123	(2.4)
Non-Black	219	(8.7)	218	(8.6)	437	(8.7)
Outside North America	2,245	(88.9)	2,245	(88.9)	4,490	(88.9)

Table 13. Subject baseline characteristics- ITT population - VICTORIA study (adapted by Rapporteur)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	2,526		2,524		5,050	
Height (cm)						
Subjects with data	2510		2497		5007	
Mean	168.0		168.0		168.0	
SD	9.9		9.8		9.9	
Median	168.0		168.0		168.0	
Range	130.0 to 202.0		114.0 to 203.2		114.0 to 203.2	
Weight (kg)						
Subjects with data	2516		2506		5022	
Mean	78.6		79.2		78.9	
SD	20.2		20.6		20.4	
Median	76.0		76.5		76.3	
Range	32.5 to 181.6		34.2 to 195.0		32.5 to 195.0	
Body Mass Index (kg/m^2)						
Subjects with data	2509		2495		5004	
Mean	27.7		27.9		27.8	
SD	5.8		6.1		5.9	
Median	26.8		26.9		26.9	
Range	14.2 to 55.6		15.1 to 63.0		14.2 to 63.0	
NT-proBNP at Randomization (pg/ml)						
Subjects with data	2414		2391		4805	
Mean	4803.7		4679.6		4741.9	
SD	7549.4		6053.6		6845.6	
Median	2803.5		2821.0		2816.0	
Range	10.0 to 175000.0		70.0 to 86155.0		10.0 to 175000.0	
eGFR Category at Randomization ($mL/min/1.73\ m^2$)						
≤30	259	(10.3)	247	(9.8)	506	(10.0)
>30 to ≤60	1,054	(41.7)	1,064	(42.2)	2,118	(41.9)
>60	1,161	(46.0)	1,174	(46.5)	2,335	(46.2)
Missing	52	(2.1)	39	(1.5)	91	(1.8)
eGFR at Randomization ($mL/min/1.73\ m^2$)						
Subjects with data	2474		2485		4959	
Mean	61.3		61.7		61.5	

SD	27.0		27.3		27.2	
Median	58.4		58.3		58.4	
Range	11.0 to 225.5		11.1 to 226.8		11.0 to 226.8	
Ejection Fraction (%) Recorded at Screening						
Subjects with data	2516		2520		5036	
Mean	29.0		28.8		28.9	
SD	8.26		8.34		8.30	
Median	30.0		29.0		30.0	
Range	6.0 to 45.0		5.0 to 45.0		5.0 to 45.0	
Ejection Fraction (%) Category Recorded at Screening						
< 30%	1.210	(47.9)	1.280	(50.7)	2.490	(49.3)
≥ 30% to < 35%	515	(20.4)	461	(18.3)	976	(19.3)
≥ 35% to < 40%	433	(17.1)	417	(16.5)	850	(16.8)
≥ 40% to ≤ 45%	358	(14.2)	362	(14.3)	720	(14.3)
Missing	10	(0.4)	4	(0.2)	14	(0.3)
Index Event						
HF Hospitalization within 3 Months	1,673	(66.2)	1,705	(67.6)	3,378	(66.9)
HF Hospitalization 3-6 Months	454	(18.0)	417	(16.5)	871	(17.2)
IV diuretic for HF (without hospitalization) within 3 Months	399	(15.8)	402	(15.9)	801	(15.9)
Time of Primary Diagnosis of Heart Failure with Reduced Ejection Fraction to Randomization (Year)						
Subjects with data	2525		2521		5046	
Mean	4.7		4.8		4.8	
SD	5.5		5.4		5.4	
Median	2.9		2.9		2.9	
Range	0.0 to 57.8		0.0 to 48.4		0.0 to 57.8	
Time of Earliest Diagnosis of Heart Failure to Randomization (with or without Reduced Ejection Fraction) (Year)						
Subjects with data	2525		2521		5046	
Mean	5.1		5.3		5.2	
SD	5.7		5.7		5.7	
Median	3.3		3.3		3.3	
Range	0.0 to 57.8		0.0 to 48.4		0.0 to 57.8	
NYHA Class at Baseline						
NYHA Class I	0	(0.0)	2	(0.1)	2	(0.0)
NYHA Class II	1,478	(58.5)	1,497	(59.3)	2,975	(58.9)
NYHA Class III	1,010	(40.0)	993	(39.3)	2,003	(39.7)
NYHA Class IV	35	(1.4)	31	(1.2)	66	(1.3)
Missing	3	(0.1)	1	(0.0)	4	(0.1)
CCSA Class at Baseline						
No Angina	2,148	(85.0)	2,147	(85.1)	4,295	(85.0)
CCSA Class 1	203	(8.0)	202	(8.0)	405	(8.0)
CCSA Class 2	121	(4.8)	123	(4.9)	244	(4.8)
CCSA Class 3	51	(2.0)	51	(2.0)	102	(2.0)
CCSA Class 4	3	(0.1)	1	(0.0)	4	(0.1)
Use of Sacubitril/Valsartan at Baseline						
Yes	360	(14.3)	371	(14.7)	731	(14.5)
No	2,161	(85.6)	2,148	(85.1)	4,309	(85.3)
Missing	5	(0.2)	5	(0.2)	10	(0.2)
History of Tobacco Use Assessed at Baseline						
Yes	1,477	(58.5)	1,495	(59.2)	2,972	(58.9)
No	1,049	(41.5)	1,029	(40.8)	2,078	(41.1)

Medical history

The most frequently reported medical history conditions other than HF included hypertension (79.1%), CAD (58.4%), hyperlipidemia (57.3%), diabetes mellitus (46.9%), atrial fibrillation (45.0%), and prior MI (42.1%). The proportions of subjects with these conditions were generally comparable in the vericiguat and placebo groups.

Background HF therapies

As previously noted, the protocol specified that all subjects were to be treated with guideline-directed medical therapies for HF therapies as tolerated, according to locally relevant guidelines. At baseline, 91.4% of subjects took 2 or more guideline-directed medical therapies for HF, and 59.7% reported use of all 3 therapies (**Table 26**). In the study, 93.1% of the subjects received beta-blockers, 87.4% of the subjects RAS inhibitors, and 70.3% of the subjects MRAs. Use of the more recently approved and commercially available ARNI, sacubitril/valsartan at baseline was reported by 14.5% of the population. Additionally, 27.8% of the population had an ICD, and 14.7% had a biventricular pacemaker. The proportions of subjects with dose reduction or discontinuation of guideline-directed medical therapy for HF during follow-up were balanced between the treatment groups. The most frequently reported reason for dose modification was subject or physician preference.

Post-hoc analyses showed regional variability in the use of guideline-directed medical therapies for HF, in part due to differences in local treatment guidelines, access to and availability of some therapies, and regional differences in physician and subject preferences. At baseline, a higher proportion of subjects in regions outside North America received MRAs compared with subjects in North America. A higher portion of subjects in North America and Western Europe were treated with ICDs and biventricular pacemakers, than in other regions. Use of sacubitril/valsartan at baseline was reported for 26.5%, 24.9%, and 17.9% of subjects in North America, Western Europe, and Asia Pacific, respectively, compared with <9% in the other regions reflective of evolving access and reimbursement in different regions during the enrolment period. These regional differences in guideline-directed medical therapies for HF use persisted through the course of the study.

Per protocol, subjects requiring treatment with long-acting nitrates or nitric oxide donors were excluded from participation in the study; however, concomitant use of short-acting nitrates for treatment of angina attacks was permitted. At baseline, 15.0% of the subjects in the vericiguat group and 13.2% of subjects in the placebo group reported using any nitrate or nitric oxide donor within 30 days prior to and on the date of randomization.

Other medication

At baseline, 2.7% of subjects were receiving sodium-glucose co-transporter-2 (SGLT2) inhibitors, and 6.0% of subjects were receiving ivabradine.

Table 14 Standard of Care for Heart Failure Treatment at Baseline

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	2526		2524		5050	
Subjects with data	2521		2519		5040	
With one or more SOC treatments	2517	(99.8)	2513	(99.8)	5030	(99.8)
With no SOC treatment	4	(0.2)	6	(0.2)	10	(0.2)
Beta Blocker						
Yes	2349	(93.2)	2342	(93.0)	4691	(93.1)
No	172	(6.8)	177	(7.0)	349	(6.9)
Reasons for not on the treatment						
Contraindication	28	(1.1)	19	(0.8)	47	(0.9)
Side Effect or Treatment Intolerance	31	(1.2)	44	(1.7)	75	(1.5)
Subject or physician preference	99	(3.9)	99	(3.9)	198	(3.9)
Other	14	(0.6)	15	(0.6)	29	(0.6)
ACE-I or ARB						
Yes	1847	(73.3)	1853	(73.6)	3700	(73.4)
No	674	(26.7)	666	(26.4)	1340	(26.6)
Reasons for not on the treatment						
Contraindication	50	(2.0)	36	(1.4)	86	(1.7)
Side Effect or Treatment Intolerance	87	(3.5)	93	(3.7)	180	(3.6)
Subject currently taking the combination of Sacubitril/Valsartan	215	(8.5)	208	(8.3)	423	(8.4)
Subject or physician preference	290	(11.5)	286	(11.4)	576	(11.4)
Other	32	(1.3)	43	(1.7)	75	(1.5)
MRA						
Yes	1747	(69.3)	1798	(71.4)	3545	(70.3)
No	774	(30.7)	721	(28.6)	1495	(29.7)
Reasons for not on the treatment						
Contraindication	62	(2.5)	71	(2.8)	133	(2.6)
Not Indicated by treatment guidelines	126	(5.0)	115	(4.6)	241	(4.8)
Side Effect or Treatment Intolerance	86	(3.4)	85	(3.4)	171	(3.4)
Subject or physician preference	458	(18.2)	408	(16.2)	866	(17.2)
Other	42	(1.7)	42	(1.7)	84	(1.7)
Sacubitril/Valsartan						
Yes	360	(14.3)	371	(14.7)	731	(14.5)
No	2161	(85.7)	2148	(85.3)	4309	(85.5)
Reasons for not on the treatment						
Contraindication	63	(2.5)	47	(1.9)	110	(2.2)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Sacubitril/Valsartan						
Not Indicated by treatment guidelines	512	(20.3)	517	(20.5)	1029	(20.4)
Side Effect or Treatment Intolerance	46	(1.8)	44	(1.7)	90	(1.8)
Subject or physician preference	928	(36.8)	884	(35.1)	1812	(36.0)
Treatment Not Available	482	(19.1)	486	(19.3)	968	(19.2)
Other	130	(5.2)	170	(6.7)	300	(6.0)
ICD						
Yes	696	(27.6)	703	(27.9)	1399	(27.8)
No	1825	(72.4)	1816	(72.1)	3641	(72.2)
Reasons for not on the treatment						
Not Indicated by treatment guidelines	842	(33.4)	831	(33.0)	1673	(33.2)
Side Effect or Treatment Intolerance	7	(0.3)	5	(0.2)	12	(0.2)
Subject or physician preference	650	(25.8)	671	(26.6)	1321	(26.2)
Treatment Not Available	192	(7.6)	182	(7.2)	374	(7.4)
Other	134	(5.3)	127	(5.0)	261	(5.2)
Biventricular Pacemaker						
Yes	370	(14.7)	369	(14.6)	739	(14.7)
No	2151	(85.3)	2150	(85.4)	4301	(85.3)
Reasons for not on the treatment						
Not Indicated by treatment guidelines	1110	(44.0)	1128	(44.8)	2238	(44.4)
Side Effect or Treatment Intolerance	7	(0.3)	5	(0.2)	12	(0.2)
Subject or physician preference	715	(28.4)	718	(28.5)	1433	(28.4)
Treatment Not Available	183	(7.3)	171	(6.8)	354	(7.0)
Other	136	(5.4)	128	(5.1)	264	(5.2)
Standard of Care Device						
No Device	1708	(67.8)	1717	(68.2)	3425	(68.0)
ICD Only	443	(17.6)	433	(17.2)	876	(17.4)
Biventricular Pacemaker Only	117	(4.6)	99	(3.9)	216	(4.3)
ICD and Biventricular Pacemaker	253	(10.0)	270	(10.7)	523	(10.4)
Any RAS Inhibitor (ACE-I or ARB or Sacubitril/Valsartan)						
Yes	2194	(87.0)	2210	(87.7)	4404	(87.4)
No	327	(13.0)	309	(12.3)	636	(12.6)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Two or more SOC Medications						
No	221	(8.8)	210	(8.3)	431	(8.6)
Yes	2300	(91.2)	2309	(91.7)	4609	(91.4)
MRA + Any RAS Inhibitor	91	(3.6)	100	(4.0)	191	(3.8)
Beta Blocker + Any RAS Inhibitor	569	(22.6)	532	(21.1)	1101	(21.8)
MRA + Beta Blocker	160	(6.3)	148	(5.9)	308	(6.1)
MRA + Beta Blocker + Any RAS Inhibitor	1480	(58.7)	1529	(60.7)	3009	(59.7)

MRA: Mineralocorticoid Receptor Antagonist.
ICD: Implantable Cardioverter-Defibrillators.
ACE-I: Angiotensin-Converting Enzyme Inhibitor.
ARB: Angiotensin II Receptor Blocker.
RAS: Renin-Angiotensin System.
SOC: Standard of Care.

Numbers analysed

All efficacy analyses were based on the ITT population that included all randomized subjects and were analyzed according to the planned treatment. Subjects without post-randomization information were censored at Day 1. The ITT population included 5050 subjects.

Outcomes and estimation

Primary endpoint

Treatment with vericiguat resulted in a 10% relative hazard reduction in the first event of CV death or HF hospitalization compared with placebo. (HR 0.90 [95% CI: 0.82, 0.98]; p=0.019)(**Table 27**). The effect of treatment with vericiguat over placebo persisted throughout the duration of the study (**Figure 5**). Over the course of the study, there was a 4.2% annualized absolute risk reduction with vericiguat versus placebo. Results of a post hoc analysis indicated that 24 patients would need to be treated over an average of 1 year to prevent 1 primary endpoint event.

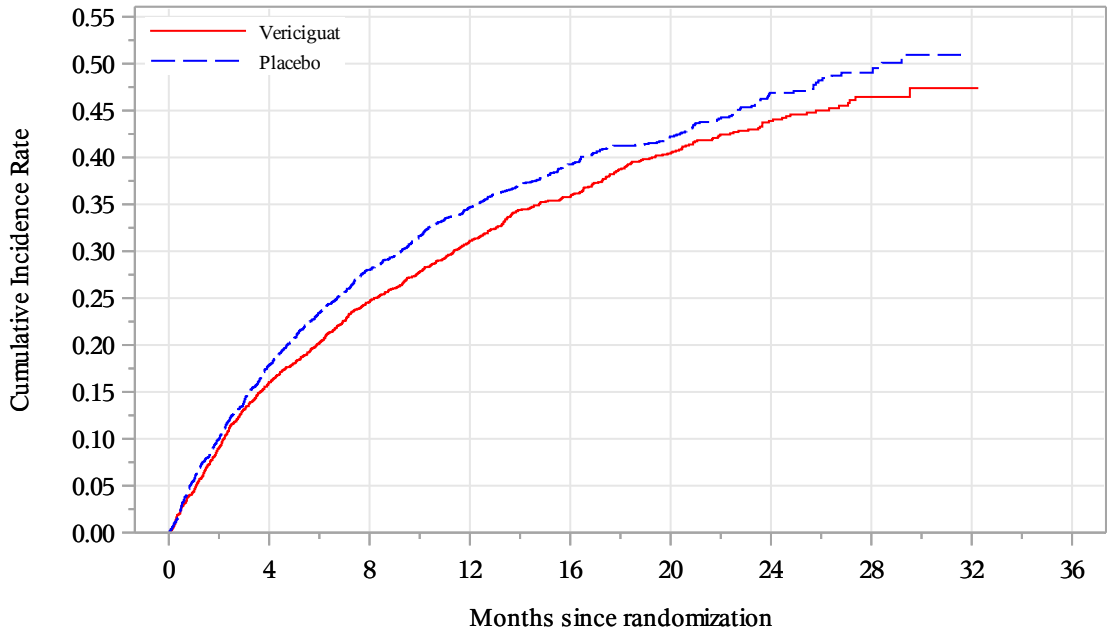
Table 27. Analysis of Primary Endpoint: Time to First Event of CEC Confirmed Cardiovascular Death or Heart Failure Hospitalization ITT Population - VICTORIA Study

	Vericiguat (N=2526)				Placebo (N=2524)				Treatment Comparison	
	n	(%)	Annual %[†]	KM% (95% CI)[‡]	n	(%)	Annual %[†]	KM% (95% CI)[‡]	HR (95% CI)[§]	p-Value[‖]
Primary Composite Endpoint	897	(35.5)	33.6	43.9 (41.5, 46.4)	972	(38.5)	37.8	46.9 (44.4, 49.4)	0.90 (0.82, 0.98)	0.019
Heart Failure Hospitalization	691	(27.4)			747	(29.6)				
Cardiovascular Death	206	(8.2)			225	(8.9)				

For subjects with multiple events, only the first event contributing to the composite endpoint is counted in the table.
[†] Total subjects with an event per 100 subject years at risk.
[‡] Kaplan-Meier estimate and confidence interval at 2 years.
[§] Hazard ratio (Vericiguat over Placebo) and confidence interval from Cox proportional hazard model controlling for stratification factors (defined by region and race).

‖ From log-rank test stratified by the stratification factors defined by region and race.
N=Number of subjects in ITT population. n=Number of subjects with an event.
Based on data up to the primary completion date (18Jun2019).

Figure 5. Kaplan-Meier Plot for Cumulative Event Rate. Primary Composite Endpoint: Time to the First Event of CEC Confirmed CV Death or Heart Failure Hospitalization ITT Population – VICTORIA Study



Number of subjects at risk

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

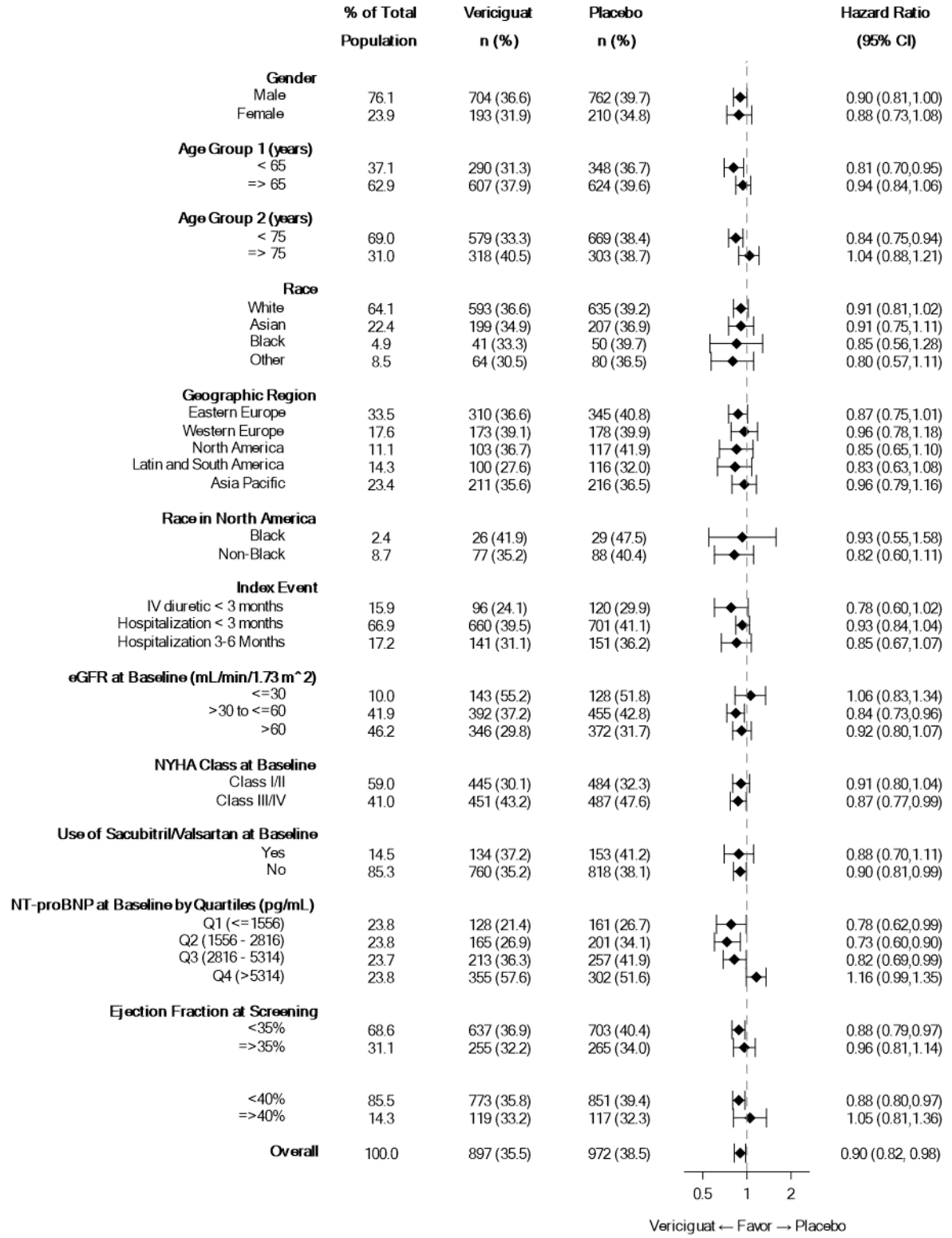
Cumulative number of events up to the time point

Vericiguat	0	402	609	733	803	857	885	896	897	897
Placebo	0	448	694	823	890	924	960	969	972	972

Subgroup analyses on the primary endpoint

The effect of vericiguat relative to placebo on the primary endpoint in the overall study population was generally consistent across prespecified subgroup factors (***Figure 6***). There were two prespecified subgroup factors for which the interaction test *p*-values for the primary composite endpoint were <0.05: Age Group 2 (<75 years vs ≥75 years; p=0.030) and baseline NT-proBNP value by quartile (p=0.001).

Figure 6. Forest plot for subgroup analysis of primary composite endpoint- ITT population- VICTORIA study



Age

The observed HR comparing vericiguat with placebo was lower for subjects less than 75 years of age at baseline compared with those 75 years of age or older. Post-hoc analyses on the HR for the primary endpoint and the secondary endpoints of CV death and HF hospitalization across the entire

distributions of age on a continuous scale showed no consistent trend for the primary endpoint or the secondary endpoints, CV death and first HF hospitalization (***Figure 7*** and ***Figure 8***).

Figure 7. Treatment Hazard Ratio (Vericiguat / Placebo) by Age (years): Time to the First Event of Heart Failure Hospitalization or Cardiovascular Death

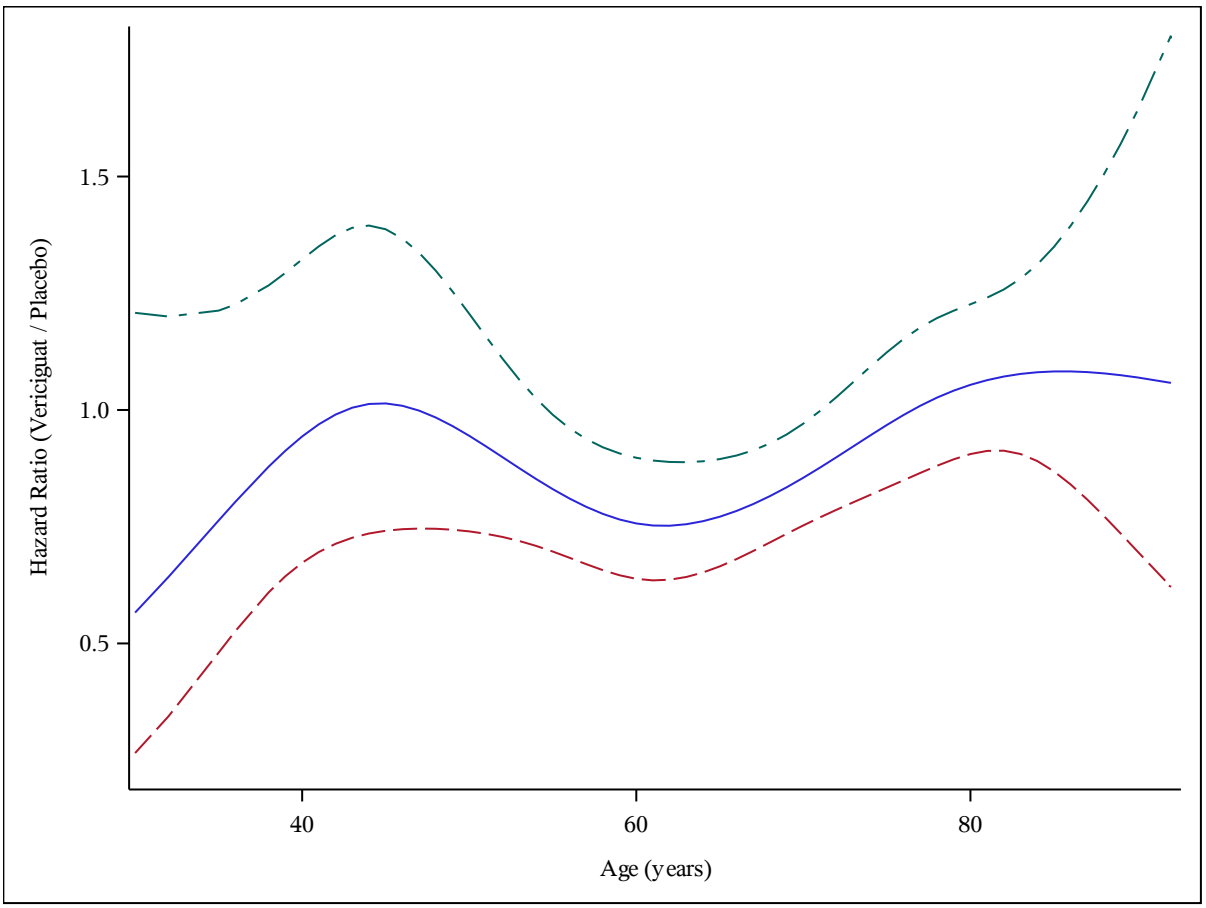
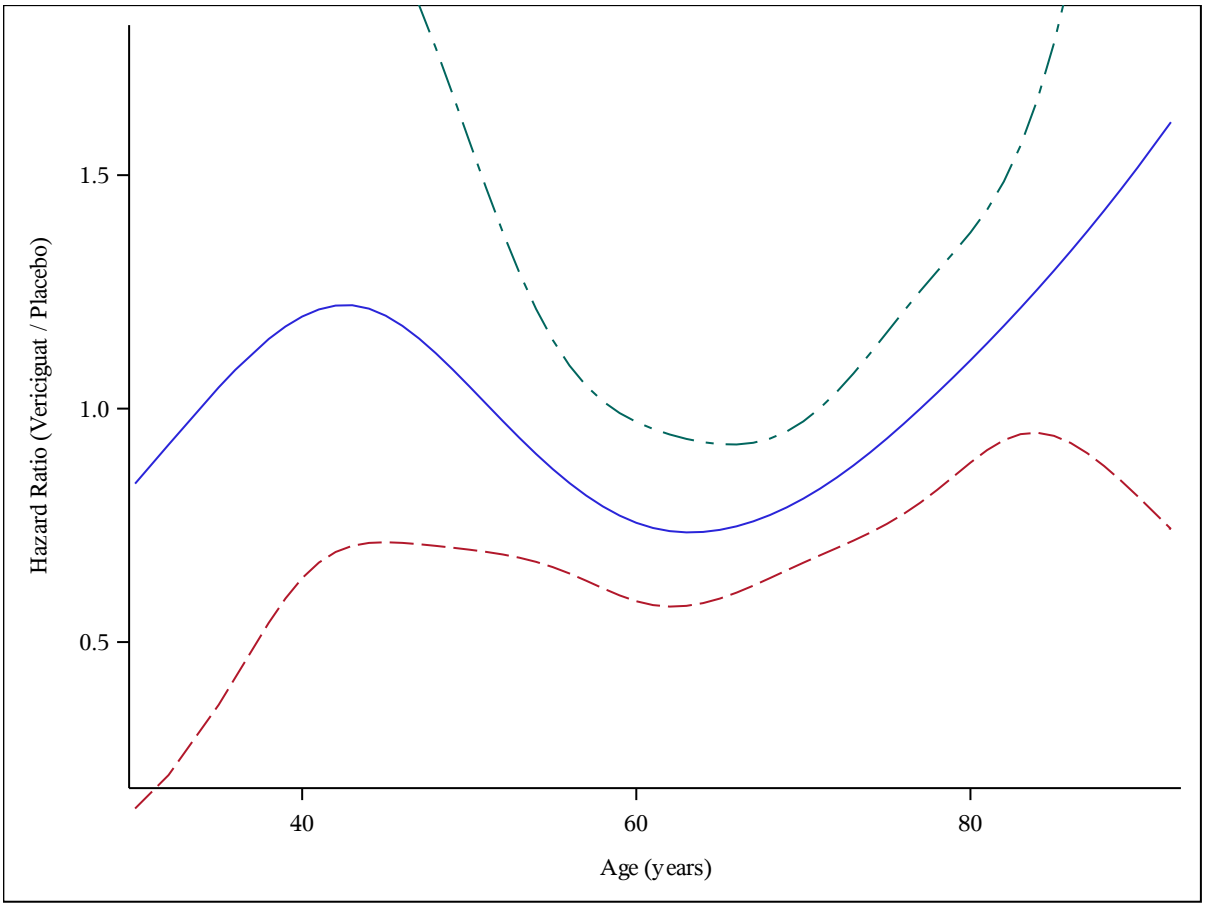


Figure 8.Treatment Hazard Ratio (Vericiguat / Placebo) by Age (years): Time to CEC Confirmed Cardiovascular Death



NT-proBNP

The observed HRs comparing vericiguat with placebo were lower for the subgroups of subjects with baseline NT-proBNP values in quartiles 1, 2, and 3 (≤5314 pg/mL) compared with those with baseline NT-proBNP values in quartile 4 (>5314 pg/mL). Post-hoc analyses across the entire distributions of NT-proBNP on a continuous scale showed that the HR for the primary endpoint increased with increasing baseline NT-proBNP (**Figure 9**). The NT-proBNP value at which the HR for the primary endpoint crossed 1 was similar to the cut point defining the fourth quartile of baseline NT-proBNP (NT-proBNP >5314 pg/mL). Similar trends across the distribution of baseline NT-proBNP values were observed for the secondary endpoints, CV death and first HF hospitalization.

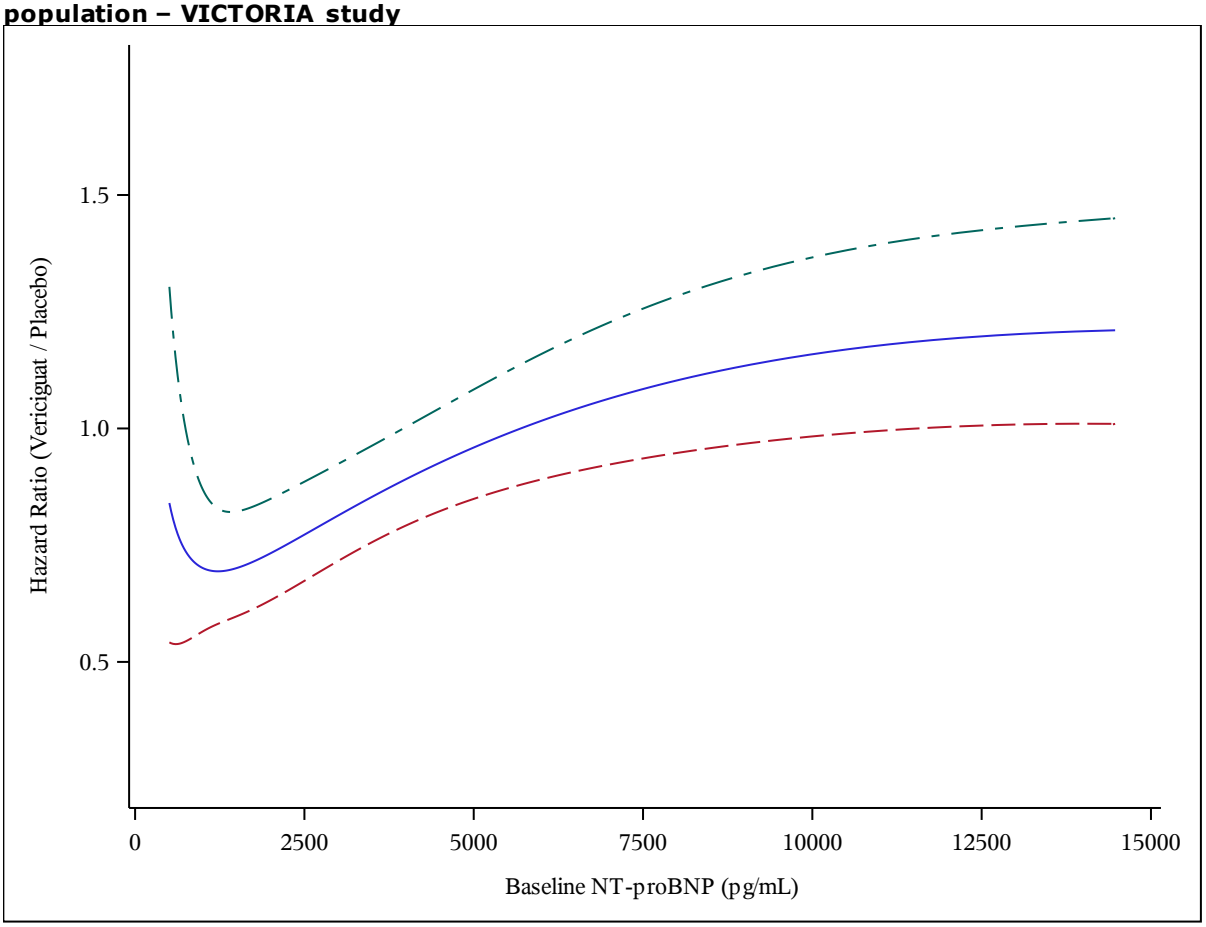
Given the interaction test p-value and further evidence of heterogeneity of effect based on baseline NT-proBNP saw in the continuous analyses above, additional post-hoc analyses were performed to further explore the findings in the subgroups defined by baseline NT-proBNP quartiles. In general, baseline characteristics were similar across NT-proBNP quartiles with small differences in age, NYHA Class, BMI, eGFR, and time from index event of HF decompensation. Specifically, those subjects with the highest NT-proBNP levels at baseline were older, had a higher NYHA Class, had a lower BMI and eGFR, and a shorter duration between their index event and randomization than those with lower NT-proBNP levels at baseline. This is consistent with previous studies showing that, in addition to HF, other factors associated with elevated natriuretic peptides include advanced age, renal dysfunction, and atrial fibrillation. No single baseline characteristic or set of characteristics appeared to uniquely define those subjects with the highest NT-proBNP in VICTORIA. A multivariate analysis (Patient Response Identifiers for Stratified Medicine [PRISM]) to identify the covariates with the strongest interactions with the treatment effect has also been conducted since the univariate analysis of

subgroups cannot discriminate genuine influences of baseline factors from indirect effects that reflect interaction by other factors. Using this model, only NT-proBNP was identified as the most influential predictor of different treatment response, whereas age and eGFR were not.

The treatment effect of vericiguat relative to placebo persisted throughout the study for subjects with baseline NT-proBNP values in quartiles 1, 2, and 3 (NT-proBNP ≤5314 pg/mL). In subjects with a baseline NT-proBNP >5314 pg/mL, the Kaplan-Meier curves for the primary endpoint and the secondary endpoints, time to CV death and time to the first HF hospitalization, showed no early separation between the vericiguat and placebo curves.

Furthermore, the median NT-proBNP value at randomization was highest in patients enrolled earlier after the index HF hospitalization, whereas in patients enrolled later (ie, > 60 days) after discharge from hospitalization, these values were lower (**Table 28**). Additionally, the HR for the composite primary endpoint of CV death and HF hospitalization was numerically lower in patients enrolled following a period of 1 to 2 months after HF hospitalization (HR 0.79) when compared to patients enrolled within 1 month after HF hospitalization (HR 1.01) (**Table 29**).

Figure 9. Treatment Hazard Ratio (Vericiguat / Placebo) by Baseline NT-proBNP (pg/mL): Time to the First Event of Heart Failure Hospitalization or Cardiovascular Death- ITT population – VICTORIA study



Hazard ratio (Vericiguat over Placebo) and confidence interval are calculated from Cox proportional hazard model with factors including treatment, stratification factor, restricted cubic splines of baseline NT-proBNP and their interactions with treatment

Table 28. NT-proBNP at randomization (pg/ml) in relation to time since discharge of the latest hospitalization

	Vericiguat	Placebo	Total
Subjects in population	2526	2524	5050
Overall population			
Subjects with Data	2414	2391	4805
Mean	4803.7	4679.6	4741.9
SD	7549.4	6053.6	6845.6
Median	2803.5	2821.0	2816.0
(Q1, Q3)	(1572.0, 5380.0)	(1548.0, 5206.0)	(1556.0, 5314.0)
Range	10.0 to 175000.0	70.0 to 86155.0	10.0 to 175000.0
Subjects randomized during index event of heart failure hospitalization			
Subjects with Data	115	114	229
Mean	8066.1	6476.0	7274.5
SD	11331.7	7104.6	9479.2
Median	4330.0	3662.0	4056.0
(Q1, Q3)	(1847.0, 8194.0)	(1602.0, 8653.0)	(1725.0, 8194.0)
Range	177.0 to 75415.0	300.0 to 35144.0	177.0 to 75415.0
Subjects discharged within 10 days prior to randomization			
Subjects with Data	381	377	758
Mean	4773.9	4753.7	4763.9
SD	4783.2	5397.4	5094.5
Median	3307.0	2958.0	3210.0
(Q1, Q3)	(1769.0, 5992.0)	(1474.0, 5630.0)	(1588.0, 5880.0)
Range	99.0 to 34025.0	190.0 to 36857.0	99.0 to 36857.0
Subjects discharged between 10-30 days prior to randomization			
Subjects with Data	579	598	1177
Mean	5054.0	4686.8	4867.4
SD	8871.5	6381.4	7706.4
Median	3028.0	2854.5	2913.0
(Q1, Q3)	(1592.0, 5852.0)	(1502.0, 5039.0)	(1561.0, 5405.0)
Range	29.0 to 175000.0	161.0 to 80561.0	29.0 to 175000.0
Subjects discharged between 30-60 days prior to randomization			
Subjects with Data	333	348	681
Mean	5441.6	4985.5	5208.5
SD	11093.0	5520.2	8699.5
Median	3102.0	3433.5	3248.0
(Q1, Q3)	(1628.0, 5680.0)	(1988.0, 6075.0)	(1811.0, 5847.0)
Range	10.0 to 175000.0	70.0 to 50920.0	10.0 to 175000.0

Table 29. Post hoc subgroup analysis of the primary composite by time after HF hospitalization at shorter intervals, or after IV diuretic for HF

Subgroup Analysis of Primary Composite Endpoint: Time to the First Event of CEC Confirmed Cardiovascular Death or Heart Failure Hospitalization
ITT Population

	Vericiguat (N=2526)			Placebo (N=2524)			Treatment Comparison	
	n/m (%)	Annual% [†]	KM% (95% CI) [‡]	n/m (%)	Annual% [†]	KM% (95% CI) [‡]	HR (95% CI) [§]	p-Value [§]
Index Event								
HF Hospitalization within 1 Month	395/956 (41.3)	42.6	51.1 (47.0, 55.4)	407/998 (40.8)	42.4	48.6 (44.7, 52.6)	1.01 (0.88,1.16)	0.230
HF Hospitalization 1-2 Months	170/445 (38.2)	37.1	46.6 (41.0, 52.7)	194/433 (44.8)	48.1	51.8 (46.0, 58.0)	0.79 (0.64,0.97)	
HF Hospitalization 2-3 Months	95/272 (34.9)	32.3	42.8 (36.0, 50.4)	100/274 (36.5)	34.7	45.7 (38.4, 53.6)	0.94 (0.71,1.24)	
HF Hospitalization 3-6 Months	141/454 (31.1)	27.1	38.4 (33.0, 44.3)	151/417 (36.2)	32.4	46.3 (40.3, 52.7)	0.85 (0.67,1.07)	
IV diuretic for HF (without hospitalization) within 3 Months	96/399 (24.1)	20.5	30.9 (25.5, 37.1)	120/402 (29.9)	26.4	38.7 (32.6, 45.5)	0.78 (0.60,1.02)	

Subgroup Analysis of Time to CEC Confirmed Cardiovascular Death
ITT Population

	Vericiguat (N=2526)			Placebo (N=2524)			Treatment Comparison	
	n/m (%)	Annual% [†]	KM% (95% CI) [‡]	n/m (%)	Annual% [†]	KM% (95% CI) [‡]	HR (95% CI) [§]	p-Value [§]
Index Event								
HF Hospitalization within 1 Month	172/956 (18.0)	14.7	24.4 (21.0, 28.2)	174/998 (17.4)	14.4	23.0 (19.7, 26.7)	1.02 (0.83,1.26)	0.404
HF Hospitalization 1-2 Months	85/445 (19.1)	15.4	23.7 (19.2, 29.1)	80/433 (18.5)	15.1	24.4 (19.4, 30.5)	1.01 (0.74,1.37)	
HF Hospitalization 2-3 Months	46/272 (16.9)	13.0	25.1 (18.7, 33.1)	46/274 (16.8)	13.3	24.5 (18.4, 32.1)	0.99 (0.66,1.49)	
HF Hospitalization 3-6 Months	65/454 (14.3)	10.8	18.8 (14.6, 23.9)	78/417 (18.7)	14.1	26.3 (21.1, 32.5)	0.78 (0.56,1.08)	
IV diuretic for HF (without hospitalization) within 3 Months	46/399 (11.5)	8.7	16.5 (12.3, 22.1)	63/402 (15.7)	12.0	21.0 (16.2, 27.0)	0.72 (0.49,1.05)	

[†] Total subjects with an event / time at risk in years.
[‡] Kaplan-Meier estimate and confidence interval at 2 years.
[§] Hazard ratio (Vericiguat over Placebo), 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.
N = Number of subjects in ITT population. n = Number of subjects with an event. m = Number of subjects in the subgroup.
Based on data up to the primary completion date (18Jun2019).

Vericiguat dose

To address the effect of vericiguat dosing on the magnitude of effect in VICTORIA, efficacy outcomes were analyzed in subgroups defined by vericiguat doses reached during the trial. The reference timepoint for reaching 10 mg in this search/retrieval strategy was Day 56 in order to capture the time after the earliest possible timepoint after the second up-titration option at the Day 28 visit. All patients were classified according to two subgroups: (1) those who achieved 10 mg and remained at that level for at least 80% of the subsequent follow-up time, (2) those who did not. All 5050 randomized patients were assigned to either of the two subgroups, including those with outcome events, before reaching the target dose of 10 mg (**Table 30**).

Table 15. Comparative analysis of the primary composite endpoint (time to CEC Confirmed CV Death or HF Hospitalization) as well as time to CV Death and time to HF hospitalization as single outcomes in the subgroup of subjects who reached the 10 mg dose of vericiguat and stayed at 10 mg for > 80% of the study period with those who did not (vericiguat vs placebo), ITT population

Subgroup Analysis of Primary Composite Endpoint:
Time to the First Event of CEC Confirmed Cardiovascular Death or Heart Failure Hospitalization - ITT Population

	Vericiguat (N=2526)			Placebo (N=2524)				Treatment Comparison
10 mg	n/m (%)	Annual % [a]	KM% (95% CI) [b]	n/m (%)	Annual % [a]	KM% (95% CI) [b]	HR (95% CI) [c]	p-Value [d]
Yes	473/1551 (30.5)	27.0	38.9 (35.9, 42.1)	519/1604 (32.4)	29.2	40.6 (37.6, 43.8)	0.93 (0.82,1.06)	0.175
No	420/968 (43.4)	46.2	51.5 (47.6, 55.5)	448/911 (49.2)	56.9	58.0 (53.9, 62.2)	0.82 (0.72,0.94)	
Subgroup Analysis of: Time to CEC Confirmed Cardiovascular Death - ITT Population								
Yes	204/1551 (13.2)	10.0	18.0 (15.6, 20.7)	217/1604 (13.5)	10.3	19.3 (16.8, 22.1)	0.98 (0.81,1.18)	0.219
No	206/968 (21.3)	17.7	27.9 (24.5, 31.8)	223/911 (24.5)	21.2	31.6 (27.8, 35.7)	0.82 (0.68,1.00)	
Subgroup Analysis of: Time to CEC Confirmed Heart Failure Hospitalization - ITT Population								
Yes	366/1551 (23.6)	20.9	31.0 (28.1, 34.1)	404/1604 (25.2)	22.8	32.1 (29.2, 35.3)	0.93 (0.80,1.07)	0.346
No	321/968 (33.2)	35.3	41.2 (37.4, 45.3)	338/911 (37.1)	43.0	47.2 (42.9, 51.8)	0.84 (0.72,0.98)	

[a] subjects with an event / time at risk in years.

[b] Kaplan-Meier (KM) estimate and confidence interval (CI) at 2 years.

[c] Hazard ratio (Vericiguat over Placebo), confidence interval, and
[d] 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.

CEC=Clinical Events Committee, CV=Cardiovascular, HR=Hazard ratio, HF=Heart failure, ITT=Intent to treat, N = Number of subjects in ITT population, n=Number of subjects with an event. m=Number of subjects in the subgroup.

Based on data up to the primary completion date (18Jun2019).

Secondary endpoint

The primary endpoint components were tested alongside the primary endpoint, without multiplicity correction, and therefore these secondary endpoints are considered exploratory. Results for the secondary endpoints were consistent with the results in the primary composite endpoint Vericiguat treatment resulted in a (**Table 31** and **Table 32**):

- A 7% relative hazard reduction in CEC confirmed CV death compared with placebo (HR 0.93 [95% CI, 0.81-1.06]; *p*=0.269 (exploratory)).
- A 10% relative hazard reduction in the first HF hospitalization compared with placebo (HR 0.90 [95% CI, 0.81-1.00]; *p*=0.048 (exploratory)).
- A significant 9% relative hazard reduction in the total events (first and recurrent) of HF hospitalization compared with placebo (HR 0.91 [95% CI, 0.84 0.99]; p=0.023).

- A significant 10% relative hazard reduction in the first event of the composite of CEC confirmed all-cause mortality or HF hospitalization compared with placebo (HR 0.90 [95% CI, 0.83 0.98]; p=0.021).
- A 5% relative hazard reduction in time to all-cause mortality compared with placebo, however, not statistically significant (HR 0.95 [95% CI, 0.84 1.07]; p=0.377).

Table 16. Primary and Key Secondary Efficacy Endpoints Annualized Absolute Risk Reduction and Number Needed to Treat ITT Population – VICTORIA Study (generated by Rapporteur)

	Vericiguat (N= 2526)			Placebo (N=2524)			Treatment comparison (Placebo-Vericiguat)			
	n	(%)	Annual %[†]	n	(%)	Annual %[†]	HR (95% CI)[‡]	p-Value[§]	Annualized Absolute Risk Reduction %[‖]	Number Needed to Treat[¶]
Primary Composite Endpoint of CV death or HF hospitalization	897	(35.5)	33.6	972	(38.5)	37.8	0.90 (0.82, 0.98)	0.019	4.18	23.9
Cardiovascular Death	414	(16.4)	12.9	441	(17.5)	13.9	0.93 (0.81, 1.06)	0.269	1.02	97.9
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)					
Heart Failure Hospitalization (first event)	691	(27.4)	25.9	747	(29.6)	29.1	0.90 (0.81, 1.00)	0.048	3.16	31.6
All-cause mortality or Heart Failure Hospitalization (first event)	957	(37.9)	35.9	1032	(40.9)	40.1	0.90 (0.83, 0.98)	0.021	4.2	23.8
Heart Failure	266	(10.5)		285	(11.3)					
Myocardial Infarction	691	(27.4)		747	(29.6)					
All-cause mortality	512	(20.3)	16.0	534	(21.2)	16.9	0.95 (0.84, 1.07)	0.377	0.9	111.1

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

[†] Total subjects with an event per 100 subject years at risk.

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

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

[‖] Difference (Placebo-Vericiguat) in annual event rate calculated as the total number of subjects with an event per 100 subject years at risk.

[¶] Calculated as 100 divided by the difference in annual event rates (Placebo-Vericiguat). NNT is the number of patients who would need to be treated over an average of 1 year to prevent 1 endpoint event.

N=Number of subjects in ITT population. n=Number of subjects with an event.. Based on data up to the primary completion date (18Jun2019).

Table 17. Secondary endpoint: Time to Total Events (First and Recurrent) of CEC Confirmed Heart Failure Hospitalization - ITT Population – VICTORIA Study

	Vericiguat (N=2526)			Placebo (N=2524)			Hazard Ratio‡ § (95% CI)	p-Value §
	n	Total Follow-up Time (years)	Annual %†	n	Total Follow-up Time (years)	Annual %†		
Total Events‖	1223	3190.7	38.3	1336	3151.0	42.4	0.91 (0.84, 0.99)	0.023
Subjects with only one event	415			431				
Subjects with only two events	160			179				
Subjects with only three events	55			75				
Subjects with ≥ four events	61			62				

† Total events per 100 subject years of follow up.

‡ Vericiguat over placebo.

§ 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.

‖ Total number of heart failure hospitalizations (first and recurrent).

N=Number of subjects in ITT population.

Based on data up to the primary completion date (18Jun2019).

Exploratory endpoints

The following prespecified exploratory and additional efficacy analyses were performed further to evaluate the efficacy of vericiguat in subjects with HFrEF.

- The hazard ratio for the time to the first event of CEC confirmed HF hospitalization or urgent HF visit was 0.89 (95% CI, 0.81 0.99).
- The point estimate of the incidence rate ratio comparing the total number of CEC confirmed HF hospitalizations was 0.90 (95% CI, 0.79 1.02).
- The point estimate of the mean number of days alive and not hospitalized for HF was greater with vericiguat treatment compared with placebo (LS mean 457.59 days vs 451.47 days, respectively; the difference in LS means: 6.11 [95% CI, -7.15 to 19.38]).
- The estimated reduction from baseline NT-proBNP at Week 32 was greater in the vericiguat group than in the placebo group (ratio of GMR of Week 32/ Baseline LS means: 0.90 [95% CI, 0.85-0.96]).

Additionally, the following post-hoc supportive exploratory endpoint was also performed to further evaluate the efficacy of vericiguat in subjects with HFrEF.

- The hazard ratio for the post-hoc exploratory endpoint, the time to the first event of CV death, HF hospitalization, or urgent HF visit, was 0.89 (95% CI, 0.82 0.98)

With respect to health-related quality of life measures, changes in KCCQ measures from baseline to week 32 were similar in subjects treated with vericiguat compared with placebo.

The estimated reduction from baseline NT-proBNP at week 32 was greater in the vericiguat group than in the placebo group (ratio of GMR of week 32/baseline LS means: 0.90 [95%CI, 0.85-0.96]; p=0.001).

Ancillary analyses

N/A

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 33. Summary of efficacy for VICTORIA

Title: A Randomized Parallel-Group, Placebo-Controlled, Double-Blind, Event-Driven, Multi-Center Pivotal Phase III Clinical Outcome Trial of Efficacy and Safety of the Oral sGC Stimulator Vericiguat in Subjects with Heart Failure with Reduced Ejection Fraction (HFrEF) - **V**er**IC**iguaT Gl**O**bal Study in Subjects with Heart Failure with **R**educed Eject**I**on Fr**A**ction (VICTORIA)			
Study identifier	Study 16493 / P001 EudraCT: 2016-000671-25		
Design	Randomized, placebo-controlled, parallel-group, multi-center, double-blind, event-driven, interventional design. This was a study to evaluate the efficacy and safety of VERICIGUAT 10 mg once daily as compared to placebo (1:1 ratio), in addition to guideline-directed HF therapy, in patients with chronic heart failure (New York Heart Association [NYHA] class II-IV) and reduced ejection fraction defined by a left ventricular ejection fraction (LVEF) <45%. Stratification was based on geographic region and race. Vericiguat starting dose of 2.5 mg was doubled on a bi-weekly basis to 5 mg, and to the final target dose of 10 mg.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Randomization to study completion. Study completion was the final study visit for each individual subject through the primary completion date of 18 JUN 2019, when all randomized subjects had complete follow-up for the primary efficacy endpoint and vital status. There was no run-in phase There was no extension phase Follow-up was from the date of the first dose of study drug to 14 days after the last dose of study drug treatment (referred to as "on-treatment"
Hypothesis	Superiority of vericiguat over placebo in addition to guideline-directed HF therapy		
Treatments groups	Vericiguat		Vericiguat 10 mg once daily, median length of follow-up for PE is 10.8 months, n= 2526
	Placebo		Placebo, median length of follow-up for PE is 10.8 months, n= 2524
Endpoints and definitions	Primary endpoint	Composite endpoint of CV death or HF hospitalization	Time to the first occurrence of the composite endpoint of CV death or HF hospitalization.
	Secondary	CV death	Time to CV death

	endpoints	First HF hospitalization	Time to first HF hospitalization
		Total HF hospitalization	Time to total HF hospitalizations (first and recurrent)
		Composite of all-cause mortality or HF hospitalization	Time to the composite of all-cause mortality of HF hospitalization
		All-cause mortality	Time to all-cause mortality
Database lock	31 October 2019		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat: includes all randomized subjects regardless of treatment status. The subjects were analysed according to the planned treatment. Subjects without any post-randomization information were censored at Day 1. All efficacy analyses were performed on the ITT population. All events were adjudicated by an independent clinical events committee (CEC). The primary analysis of efficacy included data through the primary completion date of the study (18 JUN 2019 per local time zones). This was considered the primary completion date for the study because it marked the anticipated timepoint when the protocol-specified number of 782 CEC confirmed CV death events would occur.		
Descriptive statistics and estimate variability	Treatment group	**Vericiguat**	**Placebo**
	Number of subject	**2526 (99.6%)**	**2524 (99.9%)**
	Primary composite endpoint		
	Time to first event of CV death or HF hospitalization	897 (35.5%)	972 (38.5%)
	• HF hospitalization	691 (27.4%)	747 (29.6%)
	• CV death	206 (8.2%)	225 (8.9%)
	Annual % (Total subjects with an event per 100 subject years at risk)	33.6	37.8
	Kaplan-Meier % (K-M) estimate at 2 years (95% CI)	43.9 (41.5, 46.4)	46.9 (44.4, 49.4)

Effect estimate per comparison	Primary composite endpoint	Vericiguat vs placebo	
		HR (95% CI)	0.90 (0.82, 0.98)
		p-value	0.019
		Annualized absolute risk reduction (%)	4.18

Analysis description	**Secondary endpoints**		
	Treatment group	**Vericiguat**	**Placebo**
	Time to CV death	414 (16.4%)	441 (17.5%)
	Annual %	12.9	13.9

	K-M estimate at 2 years (95% CI)	22.0 (20.0, 24.2)	23.7 (21.6, 26.0)
	HR (95%CI)	0.93 (0.81, 1.06)	
	p-value	Exploratory 0.269	
	Time to first event of HF hospitalization	691 (27.4%)	747 (29.6%)
	Annual %	25.9	29.1
	K-M estimate at 2 years (95% CI)	35.1 (32.7, 37.6)	37.5 (35.0, 40.0)
	HR (95% CI)	0.90 (0.81, 1.0)	
	p-value	Exploratory 0.048	
	Time to total events (first and recurrent) of HF hospitalization	1223	1336
	Total follow-up time (years)	3190.7	3151.0
	Annual %	38.3	42.4
	HR (95% CI)	0.91 (0.84, 0.99)	
	p-value	0.023	
	Time to first event of all-cause mortality or HF or HF hospitalization	957 (37.9%)	1032 (40.9%)
	Annual %	35.9	40.1
	K-M estimate at 2 years (95% CI)	46.1 (43.6, 48.6)	49.3 (46.9, 51.9)
	HR (95% CI)	0.90 (0.83, 0.98)	
	p-value	0.021	
	Time to all-cause mortality	512 (20.3%)	534 (21.2%)
	Annual %	16.0	16.9
	K-M estimate at 2 years (95% CI)	26.6 (24.4, 28.9)	28.3 (26.0, 30.7)
	HR (95% CI)	0.95 (0.84, 1.07)	
	p-value	0.377 NS	

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

No separate studies were performed in special patient populations.

Supportive study(ies)

N/A

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

This application is based on efficacy data from the phase II dose-finding study SOCRATES-REDUCED (Study 15371) and the pivotal phase III study VICTORIA (Study 16493).

Dose selection. The selection of the dose for the pivotal phase 3 study VICTORIA is based on the results shown in healthy subjects and the phase II dose-finding study SOCRATES-REDUCED. SOCRATES-REDUCED was a placebo-controlled, double-blind phase II dose-finding study to evaluate four regiments of vericiguat (1.25 mg, 2.5 mg, 2.5 up-titrated to 5 mg, and 2.5 uptitrated to 10 mg) over 12 weeks in patients with worsening HFrEF. The maximum dose strength was 10 mg since doses of 15 mg were not well tolerated in phase I studies with healthy subjects. A dose titration scheme is used in order to improve tolerability (e.g. hypotension) and based on the results of the multiple-dose escalation study in healthy subjects (Study 15357) a titration interval of 14 days was included in the titration since heart rate increases were still observed after 1 week of vericiguat treatment indicating that PD steady state is not reached by this time; this is plausible. The pool of the vericiguat dose groups was not statistically superior to placebo in the reduction of NT-proBNP after 12 weeks (primary endpoint). However, the secondary analysis showed a dose-response relationship in the reduction of NT-proBNP after 12 weeks in the vericiguat group, in which 2.5 mg vericiguat appears to be the minimally pharmacologic effective dose. A starting dose of 2.5 mg vericiguat titrated at 2-week intervals to a target dose of 10 mg showed the greatest reduction in NT-proBNP at 12 weeks compared with placebo. Additionally, popPK/PD analyses using data from SOCRATES-REDUCED showed that vericiguat exposure (C_{max}) was correlated with decreases in SBP after the first dose, but no exposure-response relationship between C_{max} and change in SBP during the remaining days of the titration period, indicating adaptation to vericiguat treatment.

In general, the selection of the dose regimen of 2.5 mg once daily as starting dose and a SBP-guided titration every 2 weeks to reach the target maintenance dose of 10mg once daily for the pivotal phase III study VICTORIA can be supported based on these PD data.

Design of the main clinical study (VICTORIA; Study 16493)

The inclusion criteria are reflected in the indication as proposed. Key inclusion criteria included a history of chronic HF (NYHA class II to IV), previous worsening HF event defined as previous HF hospitalization within 6 months prior to randomization or IV diuretic treatment for HF (without hospitalization) within 3 months prior to randomization, LVEF< 45% and elevated levels of natriuretic

peptides (NT-proBNP ≥1000 pg/mL or BNP ≥300 pg/mL in sinus rhythm or NT-proBNP ≥1600 pg/mL or BNP ≥500 pg/mL in atrial fibrillation). Key exclusion criteria included SBP < 100 mmHg or symptomatic hypotension, concurrent use of long-acting nitrates or nitric oxide donors, PDE5 inhibitors, or sGC stimulators. Further, although not specifically included in the inclusion/exclusion criteria, according to the protocol of VICTORIA all subjects were to receive standard of care HF treatment following locally relevant guidelines such as ACC/AHA and ESC Guidelines for the Management of Heart Failure recommendations. Investigators were to provide a rationale for all subjects who were not receiving standard of care HF treatment at the time of randomization.

The inclusion criteria of previous worsening HF and NT-proBNP elevations serve as high-risk enrichment factors enhancing the event rate. Enrichment using previous HF hospitalization and high NT-proBNP was implemented in EMPHASIS HF (eplerenone), and the CHMP considered it acceptable to extrapolate the results to the lower-risk population. Although an enrichment approach can be supported, the Applicant was asked to further justify the extrapolation of the data from the higher risk to the lower risk patients both with respect to efficacy and safety during the procedure, as also stated in the scientific advice (EMA SA, SA MEB 2015). Nevertheless, the Applicant indicated not to have the intention to extrapolate the results to a low-risk population without a decompensation event. Consequently, the proposed indication included the wording "*who had a previous decompensation event*". However, considering that decompensated heart failure often but not always leads to hospitalization and that in the VICTORIA trial "*previous HF decompensation*" was defined as HF hospitalization within 6 months prior to randomization or use of IV diuretics for HF [without hospitalization] within 3 months prior to randomization, the wording is further adapted into "*after a recent decompensation event requiring IV therapy*". The inclusion criteria of LVEF < 45% is quite pragmatic and aims mainly to compliment the other vericiguat HFpEF phase 3 study which recruits patients with LVEF >45%. The cut off can be agreed considering the lack of a standardized definition. However, final results have to support that efficacy is shown across different strata of lower cut-offs, which is not the case (see efficacy results). According to the exclusion criterion, patients were randomized, starting from 24 hours following IV treatment. This 24 h cut-off is considered too short, as, after decompensation, it would take a patient more time to establish the standard of care after stopping the IV medications and become clinically stable. The Applicant acknowledged that very likely not all patients enrolled in VICTORIA were clinically stable, due to the design of VICTORIA, which allowed the earliest possible randomization after initial hemodynamic stabilization. Therefore, a warning on initiation of vericiguat therapy only after optimised volume status and diuretic therapy, as well as other HF therapies, particularly in patients with very high NT-proBNP levels is stated in section 4.2 of the SmPC.

The design of VICTORIA generally appeared appropriate to achieve the primary objective of the study. The duration of the screening period up to 30 days is sufficient to assess the baseline status for eligibility. In the randomized, double-blind treatment period, eligible patients started with 2.5 mg vericiguat or matching placebo followed by 2 dose doublings in 2-week intervals to reach the 10 mg dose, dependent on the subject's tolerance determined by SBP and symptoms of hypotension. In general, the study treatment dose modification rules seem appropriate; however, not fully complete since details on the rules with respect to hypotension necessitating discontinuation of study drug have not been included. Nevertheless, a more strict dose modification recommendation as compared with VICTORIA is stated in the SmPC, which is endorsed. A follow-up period of 4 weeks after the last treatment dose can be considered appropriate for information on the safety of vericiguat off-treatment.

The primary endpoint was the time to the first occurrence of the composite of CV death or HF hospitalization, which is considered appropriate since it is robust and in line with the EMA Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure (CPMP/EWP/235/95) and in line with other recent studies, e.g. EMPHASIS-HF, PARADIGM-HF, DAPA-

FH. The secondary/ exploratory endpoints are clinically relevant, of which the individual components of the primary endpoint (i.e. CV death and FH hospitalization) and all-cause mortally are considered the key secondary endpoints.

Assumptions for the sample size calculation were based on the phase 2 study and other HFrEF studies. The assumed treatment effect of a 20% reduction is acceptable, although, in hindsight optimistic, only a 10% reduction was achieved. The calculation is accepted.

The randomisation and blinding procedures are acceptable.

The analysis sets and the statistical analysis of the primary and secondary endpoints are generally considered adequate. Multiplicity for the primary and secondary endpoints was handled by sequential testing, which will protect the overall type I error and is acceptable. The components of the primary composite endpoint were considered supportive and are not protected for multiplicity. Missing data were handled by censoring, assuming data will be missing at random; sensitivity analyses were planned to test this assumption; however, due to very little missing data (<0.5%), these were not performed. An interim analysis was planned at 75% of events but not performed due to faster enrollment than anticipated.

Efficacy data and additional analyses

The percentage of subjects who completed study medication was relatively low (61.7%), but approximately similar in the vericiguat and placebo group (61.4% and 62.1%, respectively). This is acceptable considering the severity of the disease and, consequently, the discontinuation due to clinical worsening. The main cause of study drug discontinuation was death, which was slightly lower in the vericiguat group compared with the placebo (14.2% and 15.3%, respectively). Discontinuations due to AE were approximately similar between both group (7.0% and 6.4%), which is reassuring. Furthermore, vericiguat appears to be well tolerated since the proportion of subjects who attained 10 mg vericiguat or matching placebo over the course of the study and the proportion of subjects who required a dose decrease at 1 or more visits or a dose interruption was approximately similar between both groups. The proportion of subjects who reached the 10 mg dose (vericiguat or matching placebo) by week 8 and stayed on the 10 mg dose for at least 80% of the treatment period was approximately similar in both groups (61.6% and 63.8% in the vericiguat group and in the placebo group, respectively). As a result, the mean average dose of study intervention was similar between the two groups (7.8 mg in the vericiguat group vs 8.0 mg (placebo equivalent)).

With respect to protocol deviations, the percentage and type of clinically important protocol deviations were relatively low and comparable between the vericiguat and placebo group (2.6 % versus 2.7%, respectively). Furthermore, one study centre was closed due to GCP non-compliance and the generated for the 8 subjects randomized at this site were included in all study analysis. Three of the 8 subjects did not meet study eligibility; however, it is unlikely that the results of these 8 out of 5000 patients had a major impact on the primary outcome.

Generally, the recruited patients reflect a population of HFrEF regarding demographics, comorbidities and guideline-directed medical therapies for HF, which are well distributed across the two treatment groups. There is an adequate representation of patients in NYHA Class II (58.9%) or III (39.7%), allowing an adequate assessment in these specific FCs. However, there is a limited representation of patients with NYHA Class IV (n= 66, 1.3%). The majority of subjects had EF< 30% (49.3%), 19.3% had EF ≥30% to <35%, 16.8% had EF ≥35% to <40%, and 14.3% had ≥40% to ≤45%. The mean NT-proBNP levels at baseline were 4741.9 pg/ml. At baseline, 91.4% of subjects were taking two or more guideline-directed medical therapies for HF, and 59.7% reported use of all three therapies (MRA + beta blocker + any RAS inhibitor [ACE-I, ARB or sacubitril/valsartan]). In this respect, 93.1% of the

subjects received beta-blockers, 87.4% of the subjects RAS inhibitors, and 70.3% of the subjects MRAs. Use of the more recently approved and commercially available ARNI, sacubitril/valsartan, at baseline was reported by 14.5% of the population. Additionally, 2.7% of subjects were receiving sodium-glucose co-transporter-2 (SGLT2) inhibitors. There is an adequate representation of subjects with cardiac devices (biventricular pacemaker and/or implantable cardioverter-defibrillator)(32.0%). Regional differences in guideline-directed medical therapies for HF are acknowledged and persisted through the course of the study. In this respect, region is used as a stratification factor, which is acceptable.

In the primary efficacy analysis, treatment with vericiguat resulted in a 10% relative hazard reduction in the first occurrence of the composite of CV death or HF hospitalization (HR 0.90 [95% CI, 0.82-0.98]; p=0.019). This effect was driven by a reduction in HF hospitalization events (p= 0.048 (exploratory)). In VICTORIA, the incidence rate reported per 100-patients years is 33.6 in vericiguat versus 37.8 in the placebo group, resulting in an annualized absolute risk reduction of 4.2%. The benefit of vericiguat treatment was seen early and was sustained for the entire study duration for the primary endpoint. Furthermore, post-hoc sensitivity analysis redefined the prespecified composite endpoint to exclude CV deaths confirmed by the CEC as having an undetermined cause was consistent with the prespecified analysis (HR 0.89 [95% CI, 0.81 0.98]). Additionally, an analysis of investigator-assessed (as opposed to CEC-confirmed) CV death (HR 0.92 [95% CI, 0.84 1.00]) was consistent with the prespecified analysis, which is confirmative. Additionally, the beneficial effect of vericiguat was further supported by SOCRATES-REDUCED, although not powered to detect differences in clinical outcomes. In this study, exploratory analyses showed a reduced risk in the composite endpoint of CV death or HF hospitalization in the 2.5 to 5 mg and 2.5 to 10 mg dose groups (HR 0.63 [95% CI: 0.30, 1.34] and HR 0.53 [95% CI: 0.25, 1.16], respectively) compared with the placebo. Similar results were found for the secondary endpoints all-cause death, CV death, CV hospitalization, and HF hospitalization.

The beneficial effect on the primary endpoint is modest and seems smaller than those found in other HF trials (HR 0.80 [95% CI: 0.73, 0.87]; p<0.001 for sacubitril/valsartan compared with enalapril in PARADIGM-HF and HR 0.74 [95% CI: 0.65, 0.85]; p<0.001 for dapagliflozin compared with placebo in DAPA-HF). Nevertheless, in VICTORIA, patients at high risk were studied, i.e. patients who had symptomatic heart failure with reduced ejection fraction and had recently been hospitalized or received intravenous diuretic therapy. Consequently, the incidence rate of 37.8 per 100 patient-years for the composite endpoint in VICTORIA was approximately 2 to 3 times higher than those observed in other recent HFrEF trials. Comparing the number needed to treat (NNT), which consider the event rates, the NNT of 24 patients per year to prevent one event is comparable with the NNT observed in other recent HF studies.

Heterogeneity of effect concerning NT-proBNP, EF, eGFR, and age was observed in the VICTORIA study. In subjects with baseline NT-proBNP values in quartile 4 (>5314 pg/ml) no effect was found (HR 1.16 [95% CI: 0.99, 1.35]); interaction test p= 0.001), whereas in the subgroups of subjects with baseline NT-proBNP values in quartile 1,2, and 3 (≤5314 pg/ml) a beneficial effect in primary composite endpoint was found with HRs larger than the overall effect. Post-hoc analysis evaluating the primary outcome as a continuous function of baseline NT-proBNP showed that the NT-proBNP value at which the HR for the primary endpoint crossed 1 was similar to the cut point defining quartile 4 of baseline NT-proBNP (NT-proBNP > 5314 pg/ml). Similarly, subgroup analyses of patients with ejection fraction ≥ 40 -< 45% (HR 1.05 [95% CI: 0.81, 1.36]), eGFR at baseline ≤ 30 ml/min/1.73 m2 (HR 1.06 [95% CI: 0.83, 1.34]), and ≥ 75 years of age (HR 1.04 [95% CI: 0.88, 1.21]) also showed no beneficial effect in the primary composite endpoint; all with a HR above 1. These observations suggested that vericiguat might not be appropriate in these more vulnerable, compromised group of patients. However, post-hoc multivariate analysis (Patient Response Identifiers for Stratified Medicine

[PRISM]) only identified NT-proBNP as the most influential predictor of different treatment responses, whereas age and eGFR were not. Data on median-NT-proBNP concerning the time after index event demonstrated the median NT-proBNP was highest in patients enrolled earlier after the index HF hospitalization, indicating that NT-proBNP is a dynamic marker usually significantly increased at a decompensation event. Additionally, the HR for the composite primary endpoint of CV death and HF hospitalization was numerically lower in patients enrolled following a period of 1-2 months after HF hospitalization (HR 0.79) when compared to patients enrolled within 1 month after HF hospitalization (HR 1.01). These findings suggest that patients with very high NT-proBNP reflect clinically unstable patients who require further optimizing of diuretic therapy, other HF therapies and volume status.

Subgroup analyses with respect to gender, race, geographic region, HF decompensation index event type, NYHA Class, and use of sacubitril/valsartan at baseline showed a consistent beneficial effect.

The components of the primary endpoint were tested alongside the primary endpoint, without multiplicity correction, and therefore these secondary endpoints are considered exploratory. The analyses showed that the significant beneficial effect in primary composite endpoint is mainly driven by a reduction in HF hospitalization events (n=691 (27.4%) and n=747 (29.6%) in the vericiguat and placebo group, respectively, HR 0.90 [95% CI: 0.81, 1.00]; p=0.048 (exploratory)). The relative risk reduction in CV death was 7% (n= 414 (16.4%) and 441 (17.5%), HR 0.93 [95% CI: 0.81, 1.06]; p=0.269 (exploratory)). Consistent with the primary composite endpoint, secondary endpoint analysis showed that treatment with vericiguat resulted in a significant relative hazard reduction of 9% in the total event (first and recurrent) HF hospitalization (HR 0.91 [95% CI, 0.84, 0.99]; p=0.023) and 10% in the composite of all-cause mortality or HF hospitalisation (HR 0.90 [95% CI, 0.83 0.98]; p=0.021) compared with placebo. Similarly, as the secondary endpoint CV death, no significant difference was found in all-cause mortality compared with placebo (HR 0.95 [95% CI, 0.84, 1.07]; p=0.377). As expected, the most common type of CV death encountered in this study was heart failure.

With respect to exploratory endpoint analysis, no clinically relevant differences in KCCQ clinical summary score were reported between the vericiguat and placebo group. Further, treatment with vericiguat resulted in a reduction in NT-proBNP compared with placebo.

2.5.4. Conclusions on the clinical efficacy

Efficacy of vericiguat at a starting dose of 2.5 up titrated to 10 mg in 2-week intervals to reach the 10 mg dose is shown to be superior to placebo in terms of CV mortality and HF hospitalisation. The application was considered approvable from clinical efficacy point of view.

2.6. Clinical safety

Main safety information for vericiguat is based on the phase III VICTORIA study, as this study represents the largest dataset in the target population. Where applicable, supportive safety data are obtained from the phase II study in heart failure with reduced ejection fraction (HFrEF) SOCRATES-REDUCED (Study 15371) and the 2 phase II studies in heart failure with preserved ejection fraction (HFpEF)(SOCRATES-PRESERVED (Study 15829) and VITALITY (Study 19334).

Patient exposure

In VICTORIA, a total of 2519 subjects with HFrEF has been exposed to any vericiguat dose and 2063 subjects with HFrEH to 10 mg vericiguat (mean duration of 375.5 days and 362.0 days, respectively).

The median length of follow-up for the primary endpoint in the ITT population was 11.1 months in the vericiguat group and 10.8 months in the placebo group (**Table 34**). The mean average dose of study intervention was 7.8 mg in the vericiguat group and 8.0 mg (placebo equivalent) in the placebo group.

In SOCRATES-REDUCED, the mean duration of treatment was 73.4 days in all treatment groups and ranged between 70.7 and 77.3 days in the vericiguat treatment groups and 72.7 days in the placebo group.

Table 18. Amount of Follow-Up for the Primary Endpoint- ITT population

	Vericiguat (N=2526)	Placebo (N=2524)	Total (N=5050)
Minimum follow-up†			
28 Days	2415	2385	4800
4 Months	2099	2053	4152
8 Months	1621	1555	3176
12 Months	1154	1097	2251
16 Months	826	772	1598
20 Months	577	559	1136
24 Months	348	324	672
Mean (SD) length of follow-up (months)	12.7 (8.4)	12.2 (8.4)	12.5 (8.4)
Median (Q1, Q3) length of follow-up (months)	11.1 (6.5, 19.1)	10.4 (6.1, 18.7)	10.8 (6.3, 18.9)
Total patient-years of follow-up‡	2668.9	2572.0	5240.9
Total potential patient-years of follow-up§	2681.2	2582.7	5263.9
% of follow-up‖	99.5	99.6	99.6

† Counts in these rows indicate the number of subjects with at least the amount of follow-up given in the first column.
‡ Computed for each subject as the day of randomization to the day of the first occurrence of a primary endpoint event, the last available information on primary endpoint event, or the primary completion date (18Jun2019).
§ Computed for each subject as the day of randomization to the day of the earlier instance of a primary endpoint event, death or the primary completion date (18Jun2019).
‖ % of follow-up = (Patient-years of follow-up / Potential patient-years of follow-up) x 100.
SD = Standard deviation; Q1 = 25th percentile; Q3 = 75th percentile.
Based on data up to the primary completion date (18Jun2019).

Source: [P001MK1242: adam-adsl; adbase]

Adverse events

In VICTORIA, treatment-emergent adverse events (TEAEs) were frequently reported, however, the percentage of subjects with any TEAE was similar between the vericiguat (80.5%) and placebo (81.0%) (**Table 35**). The percentage of subjects who experienced any treatment-emergent serious adverse event (SAE) and was slightly lower in the vericiguat group compared with the placebo group (32.8% versus 34.8%, respectively).

Table 19. Analysis of Adverse Event Summary

	Vericiguat		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	2,519		2,515		
with one or more adverse events	2,027	(80.5)	2,036	(81.0)	-0.5 (-2.7, 1.7)
with no adverse event	492	(19.5)	479	(19.0)	0.5 (-1.7, 2.7)
with drug-related[‡] adverse events	367	(14.6)	294	(11.7)	2.9 (1.0, 4.7)
with non-serious adverse events	1,935	(76.8)	1,928	(76.7)	0.2 (-2.2, 2.5)
with serious adverse events	826	(32.8)	876	(34.8)	-2.0 (-4.7, 0.6)
with serious drug-related adverse events	30	(1.2)	20	(0.8)	0.4 (-0.2, 1.0)
with dose modification[§] due to an adverse event	653	(25.9)	606	(24.1)	1.8 (-0.6, 4.2)
who died[‖]	83	(3.3)	85	(3.4)	-0.1 (-1.1, 0.9)
who died due to a drug-related adverse event	1	(0.0)	0	(0.0)	0.0 (-0.1, 0.2)
discontinued drug due to an adverse event	167	(6.6)	158	(6.3)	0.3 (-1.0, 1.7)
discontinued drug due to a drug-related adverse event	64	(2.5)	47	(1.9)	0.7 (-0.1, 1.5)
discontinued drug due to a serious adverse event	71	(2.8)	87	(3.5)	-0.6 (-1.6, 0.3)

discontinued drug due to a serious drug-related adverse event	13	(0.5)	8	(0.3)	0.2 (-0.2, 0.6)

† Based on Miettinen & Nurminen method.

‡ Determined by the investigator to be related to the drug.

§ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

‖ Includes adverse events associated with a fatal outcome but does not reflect all deaths reported in the study.

Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

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 completion date (18Jun2019).

Common TEAEs

The incidences of AEs by system organ class were generally comparable in the vericiguat and placebo groups (Table 36). The 4 AEs with the highest incidence were hypotension, cardiac failure, pneumonia, and anaemia. The most frequent AE with a greater incidence with vericiguat compared with placebo: anaemia (7.6% in the vericiguat group versus 5.7% in the placebo group), dyspepsia (2.7% versus 1.1%), nausea (3.8% versus 2.7%), and headache (3.4% versus 2.4%).

Table 20. Subjects With Adverse Events Within a System Organ Class (Incidence ≥ 2% in One or More Treatment Groups) All Subjects as Treated – VICTORIA Study

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	2,519		2,515		5,034	
with one or more adverse events	2,027	(80.5)	2,036	(81.0)	4,063	(80.7)
with no adverse events	492	(19.5)	479	(19.0)	971	(19.3)
Blood and lymphatic system disorders	**268**	**(10.6)**	**212**	**(8.4)**	**480**	**(9.5)**
Anaemia	192	(7.6)	143	(5.7)	335	(6.7)
Cardiac disorders	**583**	**(23.1)**	**645**	**(25.6)**	**1,228**	**(24.4)**
Atrial fibrillation	89	(3.5)	96	(3.8)	185	(3.7)
Cardiac failure	224	(8.9)	250	(9.9)	474	(9.4)
Ventricular tachycardia	42	(1.7)	60	(2.4)	102	(2.0)
Ear and labyrinth disorders	**68**	**(2.7)**	**54**	**(2.1)**	**122**	**(2.4)**
Endocrine disorders	**65**	**(2.6)**	**54**	**(2.1)**	**119**	**(2.4)**
Eye disorders	**90**	**(3.6)**	**106**	**(4.2)**	**196**	**(3.9)**
Gastrointestinal disorders	**637**	**(25.3)**	**546**	**(21.7)**	**1,183**	**(23.5)**

Constipation	74	(2.9)	77	(3.1)	151	(3.0)
Diarrhoea	130	(5.2)	124	(4.9)	254	(5.0)
Dyspepsia	67	(2.7)	27	(1.1)	94	(1.9)
Nausea	96	(3.8)	67	(2.7)	163	(3.2)
Vomiting	56	(2.2)	45	(1.8)	101	(2.0)
General disorders and administration site conditions	**370**	**(14.7)**	**393**	**(15.6)**	**763**	**(15.2)**
Asthenia	47	(1.9)	58	(2.3)	105	(2.1)
Chest pain	59	(2.3)	74	(2.9)	133	(2.6)
Oedema peripheral	98	(3.9)	95	(3.8)	193	(3.8)
Hepatobiliary disorders	**124**	**(4.9)**	**117**	**(4.7)**	**241**	**(4.8)**
Infections and infestations	**868**	**(34.5)**	**880**	**(35.0)**	**1,748**	**(34.7)**
Bronchitis	87	(3.5)	112	(4.5)	199	(4.0)
Cellulitis	50	(2.0)	42	(1.7)	92	(1.8)
Influenza	74	(2.9)	57	(2.3)	131	(2.6)
Infections and infestations	**868**	**(34.5)**	**880**	**(35.0)**	**1,748**	**(34.7)**
Nasopharyngitis	121	(4.8)	127	(5.0)	248	(4.9)
Pneumonia	161	(6.4)	180	(7.2)	341	(6.8)
Upper respiratory tract infection	120	(4.8)	115	(4.6)	235	(4.7)
Urinary tract infection	89	(3.5)	98	(3.9)	187	(3.7)
Injury, poisoning and procedural complications	**312**	**(12.4)**	**320**	**(12.7)**	**632**	**(12.6)**

Accidental overdose	62	(2.5)	46	(1.8)	108	(2.1)
Fall	62	(2.5)	59	(2.3)	121	(2.4)
Investigations	**360**	**(14.3)**	**389**	**(15.5)**	**749**	**(14.9)**
Blood creatinine increased	52	(2.1)	50	(2.0)	102	(2.0)
Gamma-glutamyltransferase increased	49	(1.9)	66	(2.6)	115	(2.3)
Metabolism and nutrition disorders	**543**	**(21.6)**	**603**	**(24.0)**	**1,146**	**(22.8)**
Diabetes mellitus	43	(1.7)	53	(2.1)	96	(1.9)
Gout	83	(3.3)	96	(3.8)	179	(3.6)
Hyperkalaemia	111	(4.4)	140	(5.6)	251	(5.0)
Hyperuricaemia	77	(3.1)	72	(2.9)	149	(3.0)
Hypokalaemia	94	(3.7)	87	(3.5)	181	(3.6)
Musculoskeletal and connective tissue disorders	**317**	**(12.6)**	**355**	**(14.1)**	**672**	**(13.3)**
Arthralgia	49	(1.9)	57	(2.3)	106	(2.1)
Back pain	60	(2.4)	68	(2.7)	128	(2.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**84**	**(3.3)**	**78**	**(3.1)**	**162**	**(3.2)**
Nervous system disorders	**467**	**(18.5)**	**440**	**(17.5)**	**907**	**(18.0)**
Dizziness	169	(6.7)	150	(6.0)	319	(6.3)
Headache	86	(3.4)	61	(2.4)	147	(2.9)
Syncope	101	(4.0)	88	(3.5)	189	(3.8)

Psychiatric disorders	**108**	**(4.3)**	**140**	**(5.6)**	**248**	**(4.9)**
Insomnia	33	(1.3)	52	(2.1)	85	(1.7)
Renal and urinary disorders	**435**	**(17.3)**	**435**	**(17.3)**	**870**	**(17.3)**
Acute kidney injury	134	(5.3)	127	(5.0)	261	(5.2)
Chronic kidney disease	88	(3.5)	90	(3.6)	178	(3.5)
Renal failure	92	(3.7)	89	(3.5)	181	(3.6)
Renal impairment	67	(2.7)	66	(2.6)	133	(2.6)
Reproductive system and breast disorders	**79**	**(3.1)**	**93**	**(3.7)**	**172**	**(3.4)**
Respiratory, thoracic and mediastinal disorders	**490**	**(19.5)**	**510**	**(20.3)**	**1,000**	**(19.9)**
Chronic obstructive pulmonary disease	76	(3.0)	58	(2.3)	134	(2.7)
Cough	111	(4.4)	105	(4.2)	216	(4.3)
Dyspnoea	133	(5.3)	129	(5.1)	262	(5.2)
Epistaxis	37	(1.5)	59	(2.3)	96	(1.9)
Skin and subcutaneous tissue disorders	**218**	**(8.7)**	**227**	**(9.0)**	**445**	**(8.8)**
Vascular disorders	**553**	**(22.0)**	**511**	**(20.3)**	**1,064**	**(21.1)**
Hypertension	51	(2.0)	67	(2.7)	118	(2.3)
Hypotension	388	(15.4)	354	(14.1)	742	(14.7)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

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 completion date (18Jun2019).

Treatment-related TEAEs

The incidence of drug-related AEs was 14.6% in the vericiguat group and 11.7% in the placebo group (**Table 37**). The only AE term with an incidence of ≥2% in either treatment group was hypotension (6.8% and 5.9% in the vericiguat and placebo group, respectively).

Table 21. Subjects With Drug-Related Adverse Events Within a System Organ Class (Incidence ≥ 0 % in One or More Treatment Groups) All Subjects as Treated – VICTORIA Study

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	2,519		2,515		5,034	
with one or more drug-related adverse events	367	(14.6)	294	(11.7)	661	(13.1)
with no drug-related adverse events	2,152	(85.4)	2,221	(88.3)	4,373	(86.9)
Blood and lymphatic system disorders	**1**	**(0.0)**	**2**	**(0.1)**	**3**	**(0.1)**
Anaemia	0	(0.0)	1	(0.0)	1	(0.0)
Neutropenia	0	(0.0)	1	(0.0)	1	(0.0)
Thrombocytopenia	1	(0.0)	0	(0.0)	1	(0.0)
Cardiac disorders	**15**	**(0.6)**	**5**	**(0.2)**	**20**	**(0.4)**
Angina pectoris	1	(0.0)	0	(0.0)	1	(0.0)
Cardiac failure	5	(0.2)	5	(0.2)	10	(0.2)
Cardiac failure acute	0	(0.0)	1	(0.0)	1	(0.0)
Coronary artery disease	0	(0.0)	1	(0.0)	1	(0.0)
Palpitations	2	(0.1)	0	(0.0)	2	(0.0)
Sinus bradycardia	1	(0.0)	0	(0.0)	1	(0.0)
Sinus node dysfunction	1	(0.0)	0	(0.0)	1	(0.0)
Supraventricular extrasystoles	1	(0.0)	0	(0.0)	1	(0.0)
Tachycardia	2	(0.1)	0	(0.0)	2	(0.0)
Ventricular arrhythmia	1	(0.0)	0	(0.0)	1	(0.0)
Ventricular tachycardia	2	(0.1)	0	(0.0)	2	(0.0)
Ear and labyrinth disorders	**7**	**(0.3)**	**4**	**(0.2)**	**11**	**(0.2)**
Vertigo	7	(0.3)	4	(0.2)	11	(0.2)
Endocrine disorders	**1**	**(0.0)**	**1**	**(0.0)**	**2**	**(0.0)**
Hyperthyroidism	1	(0.0)	1	(0.0)	2	(0.0)
Eye disorders	**4**	**(0.2)**	**8**	**(0.3)**	**12**	**(0.2)**
Conjunctival haemorrhage	0	(0.0)	1	(0.0)	1	(0.0)
Diplopia	1	(0.0)	0	(0.0)	1	(0.0)
Eye inflammation	1	(0.0)	0	(0.0)	1	(0.0)
Ocular hyperaemia	1	(0.0)	3	(0.1)	4	(0.1)
Vision blurred	1	(0.0)	3	(0.1)	4	(0.1)
Xanthopsia	0	(0.0)	1	(0.0)	1	(0.0)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**64**	**(2.5)**	**34**	**(1.4)**	**98**	**(1.9)**
Abdominal discomfort	2	(0.1)	1	(0.0)	3	(0.1)
Abdominal distension	1	(0.0)	4	(0.2)	5	(0.1)
Abdominal pain	0	(0.0)	3	(0.1)	3	(0.1)
Abdominal pain upper	8	(0.3)	4	(0.2)	12	(0.2)
Anal incontinence	1	(0.0)	0	(0.0)	1	(0.0)
Ascites	1	(0.0)	0	(0.0)	1	(0.0)
Constipation	1	(0.0)	4	(0.2)	5	(0.1)
Diarrhoea	7	(0.3)	5	(0.2)	12	(0.2)
Dry mouth	0	(0.0)	1	(0.0)	1	(0.0)
Dyspepsia	14	(0.6)	8	(0.3)	22	(0.4)
Dysphagia	1	(0.0)	0	(0.0)	1	(0.0)
Faeces discoloured	1	(0.0)	0	(0.0)	1	(0.0)
Flatulence	0	(0.0)	1	(0.0)	1	(0.0)
Frequent bowel movements	1	(0.0)	0	(0.0)	1	(0.0)
Gastritis	2	(0.1)	1	(0.0)	3	(0.1)
Gastrointestinal disorder	1	(0.0)	0	(0.0)	1	(0.0)
Gastrooesophageal reflux disease	9	(0.4)	0	(0.0)	9	(0.2)
Gingival bleeding	1	(0.0)	0	(0.0)	1	(0.0)
Nausea	19	(0.8)	5	(0.2)	24	(0.5)
Odynophagia	1	(0.0)	0	(0.0)	1	(0.0)
Regurgitation	1	(0.0)	0	(0.0)	1	(0.0)
Upper gastrointestinal haemorrhage	1	(0.0)	0	(0.0)	1	(0.0)
Vomiting	2	(0.1)	6	(0.2)	8	(0.2)
General disorders and administration site conditions	**23**	**(0.9)**	**19**	**(0.8)**	**42**	**(0.8)**
Asthenia	5	(0.2)	6	(0.2)	11	(0.2)
Chest discomfort	0	(0.0)	2	(0.1)	2	(0.0)
Chest pain	1	(0.0)	2	(0.1)	3	(0.1)
Drug intolerance	1	(0.0)	0	(0.0)	1	(0.0)
Fatigue	11	(0.4)	5	(0.2)	16	(0.3)
Gait disturbance	2	(0.1)	0	(0.0)	2	(0.0)
General physical health deterioration	1	(0.0)	0	(0.0)	1	(0.0)
Malaise	2	(0.1)	1	(0.0)	3	(0.1)
Oedema	0	(0.0)	1	(0.0)	1	(0.0)
Oedema peripheral	1	(0.0)	1	(0.0)	2	(0.0)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**23**	**(0.9)**	**19**	**(0.8)**	**42**	**(0.8)**
Peripheral swelling	1	(0.0)	0	(0.0)	1	(0.0)
Pyrexia	1	(0.0)	2	(0.1)	3	(0.1)
Hepatobiliary disorders	**1**	**(0.0)**	**3**	**(0.1)**	**4**	**(0.1)**
Hepatic function abnormal	0	(0.0)	1	(0.0)	1	(0.0)
Hyperbilirubinaemia	0	(0.0)	2	(0.1)	2	(0.0)
Liver injury	1	(0.0)	0	(0.0)	1	(0.0)
Immune system disorders	**1**	**(0.0)**	**1**	**(0.0)**	**2**	**(0.0)**
Hypersensitivity	1	(0.0)	1	(0.0)	2	(0.0)
Infections and infestations	**11**	**(0.4)**	**11**	**(0.4)**	**22**	**(0.4)**
Bronchitis	2	(0.1)	2	(0.1)	4	(0.1)
Cellulitis	1	(0.0)	0	(0.0)	1	(0.0)
Cystitis	1	(0.0)	0	(0.0)	1	(0.0)
Fungal skin infection	1	(0.0)	0	(0.0)	1	(0.0)
Nasopharyngitis	1	(0.0)	0	(0.0)	1	(0.0)
Periodontitis	0	(0.0)	1	(0.0)	1	(0.0)
Pharyngitis	1	(0.0)	1	(0.0)	2	(0.0)
Pneumonia	0	(0.0)	4	(0.2)	4	(0.1)
Respiratory tract infection	0	(0.0)	1	(0.0)	1	(0.0)
Sepsis	0	(0.0)	1	(0.0)	1	(0.0)
Upper respiratory tract infection	2	(0.1)	1	(0.0)	3	(0.1)
Urinary tract infection	2	(0.1)	0	(0.0)	2	(0.0)
Injury, poisoning and procedural complications	**5**	**(0.2)**	**5**	**(0.2)**	**10**	**(0.2)**
Accidental overdose	3	(0.1)	0	(0.0)	3	(0.1)
Contusion	0	(0.0)	2	(0.1)	2	(0.0)
Fall	2	(0.1)	1	(0.0)	3	(0.1)
Head injury	0	(0.0)	1	(0.0)	1	(0.0)
Wrist fracture	0	(0.0)	1	(0.0)	1	(0.0)
Investigations	**22**	**(0.9)**	**11**	**(0.4)**	**33**	**(0.7)**
Blood alkaline phosphatase increased	0	(0.0)	1	(0.0)	1	(0.0)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Investigations	**22**	**(0.9)**	**11**	**(0.4)**	**33**	**(0.7)**
Blood creatinine increased	5	(0.2)	4	(0.2)	9	(0.2)
Blood glucose increased	1	(0.0)	0	(0.0)	1	(0.0)
Blood potassium increased	1	(0.0)	1	(0.0)	2	(0.0)
Blood pressure decreased	1	(0.0)	1	(0.0)	2	(0.0)
Blood pressure diastolic decreased	0	(0.0)	1	(0.0)	1	(0.0)
Blood sodium increased	1	(0.0)	0	(0.0)	1	(0.0)
Blood uric acid increased	2	(0.1)	0	(0.0)	2	(0.0)
Gamma-glutamyltransferase increased	3	(0.1)	1	(0.0)	4	(0.1)
Glycosylated haemoglobin increased	1	(0.0)	0	(0.0)	1	(0.0)
Heart rate decreased	1	(0.0)	0	(0.0)	1	(0.0)
Hepatic enzyme increased	1	(0.0)	1	(0.0)	2	(0.0)
Mean cell volume increased	0	(0.0)	1	(0.0)	1	(0.0)
Platelet count decreased	1	(0.0)	0	(0.0)	1	(0.0)
Pulse pressure increased	1	(0.0)	0	(0.0)	1	(0.0)
Weight decreased	1	(0.0)	1	(0.0)	2	(0.0)
Weight increased	1	(0.0)	0	(0.0)	1	(0.0)
White blood cell count decreased	2	(0.1)	1	(0.0)	3	(0.1)
Metabolism and nutrition disorders	**5**	**(0.2)**	**11**	**(0.4)**	**16**	**(0.3)**
Decreased appetite	0	(0.0)	1	(0.0)	1	(0.0)
Dehydration	0	(0.0)	1	(0.0)	1	(0.0)
Diabetes mellitus	0	(0.0)	1	(0.0)	1	(0.0)
Electrolyte imbalance	0	(0.0)	1	(0.0)	1	(0.0)
Gout	1	(0.0)	1	(0.0)	2	(0.0)
Hyperkalaemia	1	(0.0)	2	(0.1)	3	(0.1)
Hyperlactacidaemia	1	(0.0)	0	(0.0)	1	(0.0)
Hyperuricaemia	2	(0.1)	2	(0.1)	4	(0.1)
Iron deficiency	0	(0.0)	2	(0.1)	2	(0.0)
Metabolic acidosis	1	(0.0)	0	(0.0)	1	(0.0)
Musculoskeletal and connective tissue disorders	**4**	**(0.2)**	**2**	**(0.1)**	**6**	**(0.1)**
Arthralgia	2	(0.1)	1	(0.0)	3	(0.1)
Enthesopathy	1	(0.0)	0	(0.0)	1	(0.0)
Gouty arthritis	0	(0.0)	1	(0.0)	1	(0.0)
Musculoskeletal pain	1	(0.0)	0	(0.0)	1	(0.0)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Nervous system disorders	**63**	**(2.5)**	**51**	**(2.0)**	**114**	**(2.3)**
Ageusia	0	(0.0)	1	(0.0)	1	(0.0)
Axonal neuropathy	1	(0.0)	0	(0.0)	1	(0.0)
Burning sensation	0	(0.0)	1	(0.0)	1	(0.0)
Carpal tunnel syndrome	0	(0.0)	1	(0.0)	1	(0.0)
Cognitive disorder	0	(0.0)	1	(0.0)	1	(0.0)
Diabetic mononeuropathy	0	(0.0)	1	(0.0)	1	(0.0)
Dizziness	37	(1.5)	22	(0.9)	59	(1.2)
Dizziness postural	0	(0.0)	5	(0.2)	5	(0.1)
Dysaesthesia	0	(0.0)	1	(0.0)	1	(0.0)
Dysgeusia	2	(0.1)	0	(0.0)	2	(0.0)
Generalised tonic-clonic seizure	0	(0.0)	1	(0.0)	1	(0.0)
Headache	10	(0.4)	9	(0.4)	19	(0.4)
Hypersomnia	0	(0.0)	1	(0.0)	1	(0.0)
Hypoaesthesia	1	(0.0)	0	(0.0)	1	(0.0)
Hypotonia	1	(0.0)	0	(0.0)	1	(0.0)
Loss of consciousness	1	(0.0)	0	(0.0)	1	(0.0)
Neuralgia	1	(0.0)	0	(0.0)	1	(0.0)
Paraesthesia	3	(0.1)	0	(0.0)	3	(0.1)
Presyncope	2	(0.1)	1	(0.0)	3	(0.1)
Somnolence	3	(0.1)	1	(0.0)	4	(0.1)
Syncope	7	(0.3)	11	(0.4)	18	(0.4)
Tremor	2	(0.1)	1	(0.0)	3	(0.1)
Tunnel vision	0	(0.0)	1	(0.0)	1	(0.0)
Psychiatric disorders	**2**	**(0.1)**	**7**	**(0.3)**	**9**	**(0.2)**
Alcohol abuse	0	(0.0)	1	(0.0)	1	(0.0)
Anxiety	1	(0.0)	0	(0.0)	1	(0.0)
Depressed mood	0	(0.0)	1	(0.0)	1	(0.0)
Depression	1	(0.0)	0	(0.0)	1	(0.0)
Illusion	0	(0.0)	1	(0.0)	1	(0.0)
Insomnia	0	(0.0)	1	(0.0)	1	(0.0)
Restlessness	0	(0.0)	1	(0.0)	1	(0.0)
Sleep disorder	0	(0.0)	2	(0.1)	2	(0.0)
Renal and urinary disorders	**20**	**(0.8)**	**13**	**(0.5)**	**33**	**(0.7)**
Acute kidney injury	8	(0.3)	6	(0.2)	14	(0.3)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Renal and urinary disorders	**20**	**(0.8)**	**13**	**(0.5)**	**33**	**(0.7)**
Chronic kidney disease	3	(0.1)	3	(0.1)	6	(0.1)
Haematuria	1	(0.0)	0	(0.0)	1	(0.0)
Nephropathy	1	(0.0)	0	(0.0)	1	(0.0)
Renal failure	5	(0.2)	2	(0.1)	7	(0.1)
Renal impairment	2	(0.1)	2	(0.1)	4	(0.1)
Stress urinary incontinence	1	(0.0)	0	(0.0)	1	(0.0)
Ureterolithiasis	1	(0.0)	0	(0.0)	1	(0.0)
Reproductive system and breast disorders	**3**	**(0.1)**	**6**	**(0.2)**	**9**	**(0.2)**
Erectile dysfunction	1	(0.0)	1	(0.0)	2	(0.0)
Erection increased	1	(0.0)	2	(0.1)	3	(0.1)
Gynaecomastia	1	(0.0)	2	(0.1)	3	(0.1)
Sexual dysfunction	0	(0.0)	1	(0.0)	1	(0.0)
Respiratory, thoracic and mediastinal disorders	**15**	**(0.6)**	**11**	**(0.4)**	**26**	**(0.5)**
Bronchospasm	0	(0.0)	1	(0.0)	1	(0.0)
Cough	3	(0.1)	3	(0.1)	6	(0.1)
Dyspnoea	8	(0.3)	3	(0.1)	11	(0.2)
Epistaxis	1	(0.0)	0	(0.0)	1	(0.0)
Nasal congestion	0	(0.0)	1	(0.0)	1	(0.0)
Oropharyngeal pain	0	(0.0)	1	(0.0)	1	(0.0)
Productive cough	1	(0.0)	2	(0.1)	3	(0.1)
Pulmonary oedema	1	(0.0)	0	(0.0)	1	(0.0)
Rhinorrhoea	1	(0.0)	1	(0.0)	2	(0.0)
Sputum increased	0	(0.0)	1	(0.0)	1	(0.0)
Skin and subcutaneous tissue disorders	**14**	**(0.6)**	**13**	**(0.5)**	**27**	**(0.5)**
Alopecia	0	(0.0)	1	(0.0)	1	(0.0)
Angioedema	0	(0.0)	1	(0.0)	1	(0.0)
Blister	1	(0.0)	0	(0.0)	1	(0.0)
Dermatitis bullous	0	(0.0)	1	(0.0)	1	(0.0)
Diabetic foot	0	(0.0)	1	(0.0)	1	(0.0)
Dry skin	0	(0.0)	1	(0.0)	1	(0.0)
Eczema nummular	1	(0.0)	0	(0.0)	1	(0.0)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**14**	**(0.6)**	**13**	**(0.5)**	**27**	**(0.5)**
Erythema	2	(0.1)	1	(0.0)	3	(0.1)
Hyperhidrosis	1	(0.0)	1	(0.0)	2	(0.0)
Pruritus	3	(0.1)	2	(0.1)	5	(0.1)
Pruritus generalised	0	(0.0)	1	(0.0)	1	(0.0)
Psoriasis	1	(0.0)	1	(0.0)	2	(0.0)
Rash	5	(0.2)	1	(0.0)	6	(0.1)
Rash generalised	0	(0.0)	1	(0.0)	1	(0.0)
Rash pruritic	1	(0.0)	0	(0.0)	1	(0.0)
Skin discolouration	1	(0.0)	0	(0.0)	1	(0.0)
Swelling face	1	(0.0)	0	(0.0)	1	(0.0)
Urticaria	0	(0.0)	1	(0.0)	1	(0.0)
Vascular disorders	**182**	**(7.2)**	**157**	**(6.2)**	**339**	**(6.7)**
Circulatory collapse	1	(0.0)	0	(0.0)	1	(0.0)
Diabetic vascular disorder	0	(0.0)	1	(0.0)	1	(0.0)
Flushing	1	(0.0)	1	(0.0)	2	(0.0)
Haematoma	1	(0.0)	0	(0.0)	1	(0.0)
Hypertension	0	(0.0)	1	(0.0)	1	(0.0)
Hypotension	172	(6.8)	149	(5.9)	321	(6.4)
Orthostatic hypotension	14	(0.6)	8	(0.3)	22	(0.4)

Every subject is counted a single time for each applicable row and column.
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 completion date (18Jun2019).

<u>*AEs of special interest*</u>

Hypotension and symptomatic hypotension

In VICTORIA, the percentage of subjects with a hypotension AE was 15.4% in the vericiguat group compared with 14.1% in the placebo group, of which 6.8% in the vericiguat and 5.9% in the placebo group were considered drug-related adverse events. The incidences in serious adverse events of hypotension were 1.3% in the vericiguat and 1.7% in the placebo group, of which 0.4% in each treatment group were considered serious drug-related adverse events of hypotension. The percentage of subjects who discontinued the study drug due to hypotension was slightly higher in the vericiguat group compared with the placebo group (1.9% versus 1.3%, respectively).

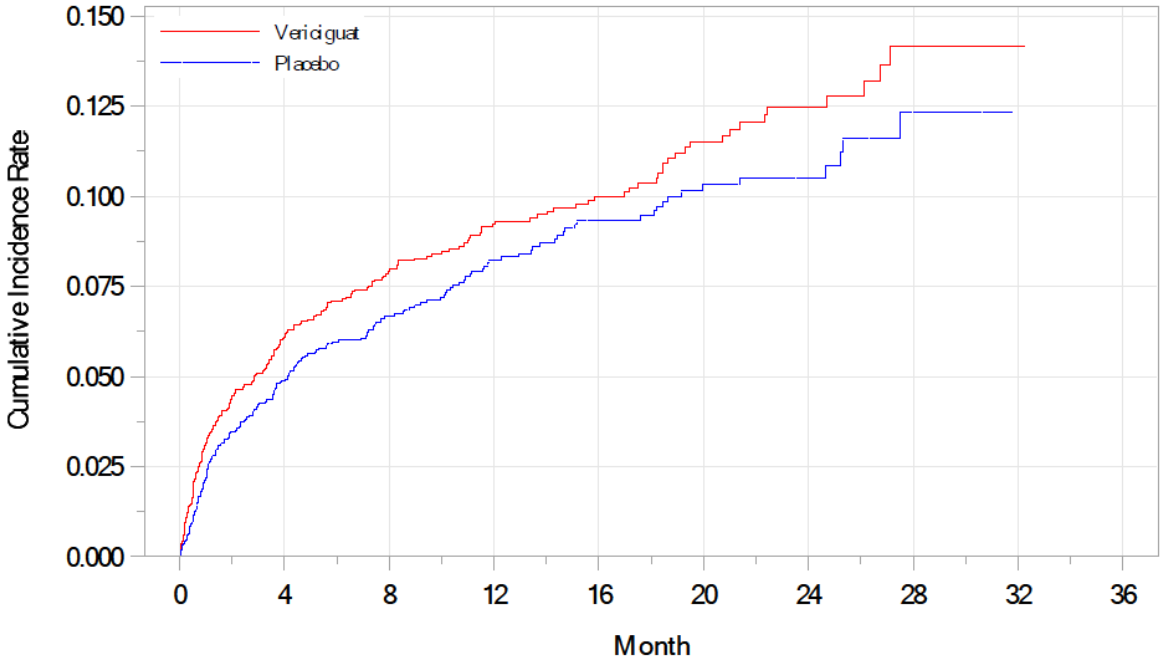
The percentage of subjects with orthostatic hypotension AE was 1.3% in the vericiguat group compared with 1.0 in the placebo group of which 0.6% in the vericiguat and 0.3% in the placebo group were considered drug-related adverse events. The incidences in serious adverse events of orthostatic hypotension were 0.2% (n=6) in the vericiguat and 0% (n=1) in the placebo group, of which only the event in the placebo group was considered a serious drug-related adverse event.

The adverse events determined by the investigator to be events of symptomatic hypotension were reported in 9.1% of subjects treated with vericiguat and 7.9% of subjects treated with placebo and were considered serious in 1.2% of subjects treated with vericiguat and 1.5% of subjects treated with placebo, of which 0.4% for vericiguat and 0.3% for placebo were considered serious drug-related adverse events. Analyses of events, which may have occurred as a consequence of symptomatic hypotension or syncope, such as falls and subsequent fractures, showed no difference between the treatment groups.

Symptomatic hypotension event rates were highest during the first 4 months following randomization for subjects in both treatment groups. The difference between vericiguat and placebo event rates occurred early and persisted throughout the study (**Figure 10**).

In the prespecified baseline subgroups of CCSA class, NYHA class, and use of sacubitril/valsartan, the proportions of subjects who experienced symptomatic hypotension were similar between the treatment groups (**Figure 11**). Furthermore, subgroups analyses of patients above 75 years of age, patients with moderate renal impairment, patients not using MRAs at baseline, and patients with systolic BP at baseline of < median showed that these patients were not more vulnerable to the hypotensive effect of vericiguat.

Figure 10. Kaplan-Meier plot for Cumulative Event Rate- Cumulative Incidence Rate of Adverse Events of Clinical Interest: Symptomatic Hypotension- All Subjects as Treated



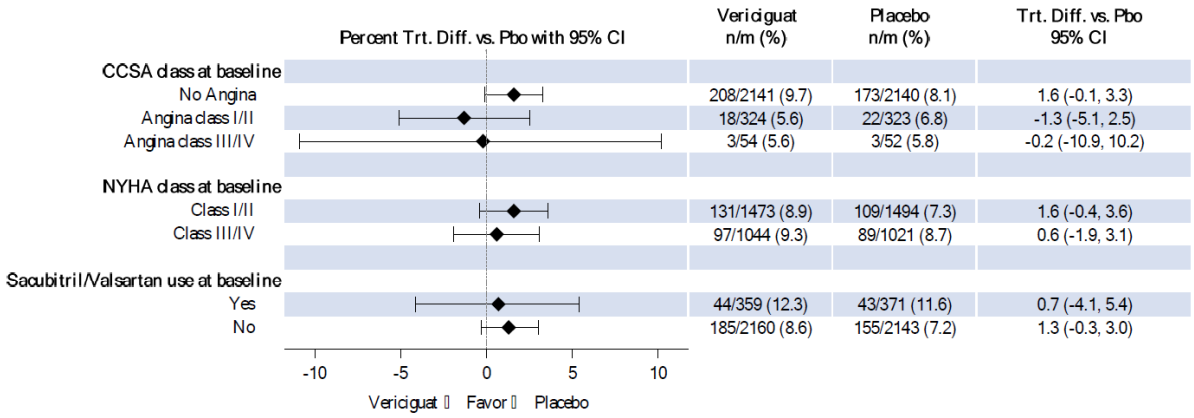
Subjects at Risk

Vericiguat	2519	2034	1574	1112	803	554	326	118	1	0
Placebo	2515	2075	1586	1098	784	545	309	101	0	0

Cumulative number of events

Vericiguat	0	146	182	201	209	220	225	229	229	229
Placebo	0	117	153	175	186	193	194	198	198	198

Figure 11. Forest Plot for Subgroup Analysis of Adverse Event of Clinical Interest of Symptomatic Hypotension- All subjects as treated



The proportion of subjects with symptomatic hypotension was the highest at the 10 mg target dose level; however, it was comparable in the vericiguat (5.4%) and the placebo (5.2%) groups (**Table 38**). A slightly higher proportion of subjects were reported in the vericiguat group when compared with placebo during titration at the 5.0 mg (vericiguat: 2.1%; placebo: 1.5%) and the 2.5 mg (vericiguat: 3.3%; placebo: 2.4%) dose levels.

Table 38. Number of subjects and events – adverse events of clinical interest symptomatic hypotension on each dose level (data through the primary completion, all subjects as treated analysis)

	Vericiguat		**Placebo**	
	n/N (%)	**Number of events**	**n/N (%)**	**Number of events**
Any event	229/ 2519 (9.1%)	292	198/ 2515 (7.9%)	252
Dose/Sham				
2.5 mg	84/ 2517 (3.3%)	90	60/ 2515 (2.4%)	70
5 mg	48/ 2285 (2.1%)	58	35/ 2297 (1.5%)	37
10 mg	111/ 2063 (5.4%)	131	110/ 2114 (5.2%)	128
Interruption	13/ 1542 (0.8%)	13	17/ 1571 (1.1%)	17

This table includes treatment-emergent events which are defined as event that started or worsened after start of study medication until last intake of study medication plus 14 days.
Events were identified based on investigator's assessment.
In case no sufficient time information is available to decide whether an event occurred before or after dose modification, the event was assigned to the higher dose.
Each subject was counted once in each dose level he/she passed.

n/N=Number of subjects

In SOCRATES-REDUCED, a high incidence of hypotensive events was reported in the highest vericiguat dose group (15.4%) compared with the placebo group (6.5%), the 1.25-mg group (5.5.%), the 2.5-mg group (6.7%), and the 2.5- to 5-mg group (4.4%), of which 8.8% in the highest vericiguat group compared with 4.3% the placebo group, 2.2% each in the 1.25 mg, 2.5mg group and the 2.5 to 5 mg group were considered to study drug-related adverse events.

Syncope

In VICTORIA, the percentage of subjects with a syncope AE was slightly higher in the vericiguat group compared with the placebo group (4.0% versus 3.5%). The incidence in syncope considered by the investigator to be drug-related was similar between the groups (0.3% n=7 and 0.4% n=11 in the vericiguat and placebo group, respectively). Further, the proportions of subjects who experienced syncope categorized as an SAE was slightly higher, 1.7% in the vericiguat group (1.7%) compared with the placebo group (1.3%) of which 0.1% in each group was considered a serious drug-related adverse event.

In SOCRATES-REDUCED, the highest incidence of syncope TEAEs was in the highest-dose vericiguat 2.5 to 10-mg group (4.4%) compared with 1 or 2 subjects in the low dose vericiguat groups or the placebo group, of which 2.2% in the highest vericiguat group compared with 0% in each the placebo group and 1.25 mg group, and the 2.5 to 5 mg and 1.1% in the 2.5mg group were considered study drug-related adverse events.

Hepatic events/ liver function tests

The proportion of subjects with hepatic adverse events was low but slightly higher in the vericiguat group compared with the placebo group (0.9% versus 0.5%). The proportion of subjects with serious hepatic adverse event was very low (15 subjects [0.6%] in the vericiguat group and 7 subjects [0.3%] in the placebo group). None of the hepatic adverse events were considered related to study medication. Furthermore, no clinically relevant differences in liver enzymes were observed (see laboratory findings).

Anaemia

The AE of anaemia was more frequently reported in the vericiguat group compared with the placebo group (7.6% versus 5.7%, respectively). The incidence in anaemia considered by the investigator to be drug-related was similar between the groups (0% n=0 and 0% n=1 in the vericiguat and placebo group, respectively). The proportion of subjects who reported SAEs with the preferred term of anaemia was low (total 1.2%; 1.6% in the vericiguat group and 0.9% in the placebo group). No serious drug-related AEs with the preferred term of anaemia were reported.

The mechanism for the higher percentage of anaemia AEs in the vericiguat group is not well understood, but anaemia has been previously reported with another sGC stimulator.

GI disorders

Treatment-emergent gastrointestinal disorders were more frequently reported in the vericiguat group compared with the placebo group (25.3% versus 21.7%, respectively of the subjects in the placebo group (**Table 36**). The most common AEs with a higher rate in the vericiguat group compared to placebo were: diarrhoea (5.2% versus 4.9%), nausea (3.8% versus 2.7%), dyspepsia (2.7% versus 1.1%), vomiting 2.2% versus 1.8%), and gastroesophageal reflux disease (1.7% versus 0.7%). The percentage of subjects with drug-related adverse events were 0.3% versus 0.2 % for diarrhoea, 0.8% versus 0.2% for nausea, 0.6% versus 0.3% for dyspepsia, 0.1% versus 0.2% for vomiting, and 0.4%

versus 0% for gastroesophageal reflux disease. No SAEs drug-related AEs of diarrhoea, nausea, dyspepsia, vomiting, and gastroesophageal reflux disease were reported.

Acute renal injury

In VICTORIA, the incidence of acute kidney injury was approximately similar between the vericiguat group and the placebo group (5.3% (n=134) versus 5.0% (n=127), respectively). Acute kidney injury considered related by study drug was reported in 8 subjects (0.3%) in the vericiguat group and 6 subjects (0.2%) in the placebo group.

In SOCRATES-REDUCED, acute renal (kidney) injury was reported by a total of 12 subjects (2.6%): 3 subjects (3.3%) in the placebo group, 3 subjects (3.3%) in the 1.25 mg group, 2 subjects (2.2%) in the 2.5 mg group, 1 subject in the 2.5-5 mg group, and 3 subjects (3.3%) in the 2.5-10 mg group. All of these events were SAEs except for 1 event in the 1.25-mg group; none resulted in a fatal outcome.

Bone disorders

Undesirable effects were observed on growing bone in non-clinical studies in adolescent rapidly-growing rats (effects not observed after chronic administration of vericiguat to adult rats and almost full-grown dogs). The safety and efficacy of vericiguat in children and adolescents aged below 18 years have not yet been established. No clinical data are available. A mechanistic study with another agent of the same pharmacological class, riociguat, performed with healthy male volunteers did not indicate a risk for riociguat-related effects on bone metabolism. Furthermore, post-marketing safety data with riociguat gave no evidence for an increased risk of adverse events on the bone. Moreover, although limited, safety data of the main part of a 6 months open label uncontrolled study with the sGC stimulator riociguat in children aged 6 to <18 years with PAH (PATENT-CHILD), did not show bone and/or growth anomalies in this population. The effects on bone metabolism in nonclinical studies with vericiguat are described in sections 4.2 and 5.3 of the SmPC.

Serious adverse events and deaths

Serious adverse event/deaths/other significant events

Serious adverse events

The proportions of subjects with SAEs were slightly higher in the vericiguat group than the placebo group (32.8% versus 34.8%, respectively) (**Table 3939**). The only SAE preferred terms reported with an incidence of ≥2% in either treatment group were pneumonia, cardiac failure, and acute kidney injury. There were no serious drug-related AEs with an incidence of ≥2% reported in either treatment group (**Table 40**).

Table 39. Subjects with serious adverse events within a system organ class (incidence ≥ 2% in one or more treatment groups) All subjects as treated – VICTORIA Study

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	2,519		2,515		5,034	
with one or more serious adverse events	826	(32.8)	876	(34.8)	1,702	(33.8)

with no serious adverse events	1,693	(67.2)	1,639	(65.2)	3,332	(66.2)
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)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**50**	**(2.0)**	**48**	**(1.9)**	**98**	**(1.9)**
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)**

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

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 completion date (18Jun2019).

Table 22. Subjects With Serious Drug-Related Adverse Events Within a System Organ Class (Incidence > 0% in One or More Treatment Groups)- All Subjects as Treated

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	2,519		2,515		5,034	
with one or more serious drug-related adverse events	30	(1.2)	20	(0.8)	50	(1.0)
with no serious drug-related adverse events	2,489	(98.8)	2,495	(99.2)	4,984	(99.0)
Cardiac disorders	**2**	**(0.1)**	**1**	**(0.0)**	**3**	**(0.1)**
Cardiac failure	0	(0.0)	1	(0.0)	1	(0.0)
Ventricular tachycardia	2	(0.1)	0	(0.0)	2	(0.0)
Gastrointestinal disorders	**2**	**(0.1)**	**0**	**(0.0)**	**2**	**(0.0)**
Gingival bleeding	1	(0.0)	0	(0.0)	1	(0.0)
Upper gastrointestinal haemorrhage	1	(0.0)	0	(0.0)	1	(0.0)
Hepatobiliary disorders	**1**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**
Liver injury	1	(0.0)	0	(0.0)	1	(0.0)
Injury, poisoning and procedural complications	**1**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**
Fall	1	(0.0)	0	(0.0)	1	(0.0)
Investigations	**1**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**
Blood creatinine increased	1	(0.0)	0	(0.0)	1	(0.0)
Metabolism and nutrition disorders	**2**	**(0.1)**	**1**	**(0.0)**	**3**	**(0.1)**
Gout	1	(0.0)	1	(0.0)	2	(0.0)

Hyperkalaemia	1	(0.0)	0	(0.0)	1	(0.0)
Metabolic acidosis	1	(0.0)	0	(0.0)	1	(0.0)
Musculoskeletal and connective tissue disorders	**1**	**(0.0)**	**1**	**(0.0)**	**2**	**(0.0)**
Enthesopathy	1	(0.0)	0	(0.0)	1	(0.0)
Gouty arthritis	0	(0.0)	1	(0.0)	1	(0.0)
Nervous system disorders	**6**	**(0.2)**	**4**	**(0.2)**	**10**	**(0.2)**
Axonal neuropathy	1	(0.0)	0	(0.0)	1	(0.0)
Cognitive disorder	0	(0.0)	1	(0.0)	1	(0.0)
Nervous system disorders	**6**	**(0.2)**	**4**	**(0.2)**	**10**	**(0.2)**
Dizziness	2	(0.1)	0	(0.0)	2	(0.0)
Generalised tonic-clonic seizure	0	(0.0)	1	(0.0)	1	(0.0)
Presyncope	1	(0.0)	0	(0.0)	1	(0.0)
Syncope	2	(0.1)	2	(0.1)	4	(0.1)
Renal and urinary disorders	**9**	**(0.4)**	**5**	**(0.2)**	**14**	**(0.3)**
Acute kidney injury	5	(0.2)	4	(0.2)	9	(0.2)
Chronic kidney disease	2	(0.1)	0	(0.0)	2	(0.0)
Haematuria	1	(0.0)	0	(0.0)	1	(0.0)
Nephropathy	1	(0.0)	0	(0.0)	1	(0.0)
Renal failure	1	(0.0)	1	(0.0)	2	(0.0)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**2**	**(0.1)**	**2**	**(0.0)**

Angioedema	0	(0.0)	1	(0.0)	1	(0.0)
Dermatitis bullous	0	(0.0)	1	(0.0)	1	(0.0)
Vascular disorders	**9**	**(0.4)**	**9**	**(0.4)**	**18**	**(0.4)**
Hypotension	9	(0.4)	9	(0.4)	18	(0.4)
Orthostatic hypotension	0	(0.0)	1	(0.0)	1	(0.0)

Every subject is counted a single time for each applicable row and column.

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 completion date (18Jun2019).

Deaths

All deaths, including CV and non-CV death, were submitted for adjudication. Study endpoints prespecified in the protocol, including CV and non-CV death, were not reported as SAEs.

The incidence in death in the vericiguat group was 20.3% (n=512) compared with 21.2% (n= 534) in the placebo group (HR 0,95 (95%CI: 0.84, 1.07); p=0.377).

Laboratory findings

Haematology

Changes from baseline over time for haemoglobin or hematocrit parameters showed no clinically meaningful differences in mean or median values between vericiguat and placebo treatment groups. During the study, the proportions of subjects who met predefined limits of change (PDLC) criteria (predefined increases and decreases) for haemoglobin and hematocrit were higher in the vericiguat group (haemoglobin 5.0%, hematocrit 3.9%) compared with the placebo group (haemoglobin 2.2%, hematocrit 3.2%) (**Table 41**).

Table 23. Subjects With Hematology Findings That Met Predetermined Criteria All Subjects as Treated - All Data Through Last Study Visit

Criteria	Vericiguat		Placebo		Total	
	n/m	(%)	n/m	(%)	n/m	(%)
Hematocrit (%)						
Decrease by 10 Percentage Points and value < LLN	81/2057	(3.9)	46/2092	(2.2)	127/4149	(3.1)
Hemoglobin (g/dL)						
Decrease ≥3.0 g/dL and value < LLN	103/2057	(5.0)	66/2092	(3.2)	169/4149	(4.1)
Leukocytes (10^9/L)						
Decrease ≥50% and value < LLN	15/2057	(0.7)	13/2092	(0.6)	28/4149	(0.7)
Increase ≥20% and value > ULN	105/2057	(5.1)	115/2092	(5.5)	220/4149	(5.3)
Platelets (10^9/L)						
Decrease ≥25% and value < LLN	65/1998	(3.3)	74/2023	(3.7)	139/4021	(3.5)
Increase ≥100% and value > ULN	11/1998	(0.6)	13/2023	(0.6)	24/4021	(0.6)

n = Number of subjects with postbaseline test results that met predetermined criteria.
m = Number of subjects with at least one postbaseline test result.
Increases and decreases are relative to baseline.
LLN = Lower limit of normal; ULN = Upper limit of normal; WBC = white blood cell;
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 completion date (18Jun2019).

Source: [P001MK1242: adam-adsl; adlb]

Clinical chemistry

The proportions of subjects who met predefined limits of change (PDLC) criteria for eGFR, creatinine and urate were slightly higher in the vericiguat group compared with the placebo group, although not considered clinically relevant (**Table 42**).

Table 24. Criteria Subjects With Blood Chemistry Findings That Met Predetermined Criteria All Subjects as Treated - All Data Through Last Study Visit

Criteria	Vericiguat		Placebo		Total	
	n/m	(%)	n/m	(%)	n/m	(%)
eGFR (mL/min/1.73 m2)						
Decrease ≥25%	575/2126	(27.0)	544/2168	(25.1)	1119/4294	(26.1)
Decrease≥50%	75/2126	(3.5)	63/2168	(2.9)	138/4294	(3.2)
Creatinine (mg/dL)						
Increase ≥0.5 mg/dL	390/2126	(18.3)	355/2168	(16.4)	745/4294	(17.3)
Increase ≥1.0 mg/dL	95/2126	(4.5)	81/2168	(3.7)	176/4294	(4.1)
Bilirubin (mg/dL)						
value ≥ 2 x ULN	70/2159	(3.2)	75/2193	(3.4)	145/4352	(3.3)
Urate (mg/dL)						
Increase ≥50% and value > ULN	142/2121	(6.7)	130/2160	(6.0)	272/4281	(6.4)
Sodium (mEq/L)						
Decrease ≥10 mEq/L and value < LLN	25/2128	(1.2)	27/2167	(1.2)	52/4295	(1.2)
Increase ≥10 mEq/L and value > ULN	6/2128	(0.3)	6/2167	(0.3)	12/4295	(0.3)
Potassium (mEq/L)						
Decrease ≥1.0 mEq/L and value < LLN	35/2102	(1.7)	47/2144	(2.2)	82/4246	(1.9)
Increase ≥1.0 mEq/L and value > ULN	119/2102	(5.7)	133/2144	(6.2)	252/4246	(5.9)
Calcium (mg/dL)						
Decrease ≥1.0 mg/dL and value < LLN	37/2126	(1.7)	37/2166	(1.7)	74/4292	(1.7)
Increase ≥1.0 mg/dL and value > ULN	14/2126	(0.7)	5/2166	(0.2)	19/4292	(0.4)

n = Number of subjects with postbaseline test results that met predetermined criteria.
m = Number of subjects with at least one postbaseline test result.
Increases and decreases are relative to baseline.
LLN = Lower limit of normal; ULN = Upper limit of normal; BUN = blood urea nitrogen; AST = aspartate aminotransferase; ALT = alanine aminotransferase;
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 completion date (18Jun2019).

Source: [P001MK1242: adam-adsl; adlb]

Liver enzymes

The incidences of elevations in ALT and AST with or without bilirubin elevations were generally similar between the treatment groups across the different range of elevations (**Table 43**).

Table 25. Subjects With Liver Function Laboratory Findings That Met Predetermined Criteria All Subjects as Treated - All Data Through Last Study Visit

Criteria	Vericiguat		Placebo		Total	
	n/m	(%)	n/m	(%)	n/m	(%)
Subjects in population	2519		2515		5034	
Alanine Aminotransferase						
≥3 x ULN	14/2157	(0.6)	21/2192	(1.0)	35/4349	(0.8)
≥5 x ULN	5/2157	(0.2)	8/2192	(0.4)	13/4349	(0.3)
≥10 x ULN	2/2157	(0.1)	1/2192	(0.0)	3/4349	(0.1)
≥20 x ULN	1/2157	(0.0)	1/2192	(0.0)	2/4349	(0.0)
Aspartate Aminotransferase						
≥3 x ULN	10/2157	(0.5)	11/2192	(0.5)	21/4349	(0.5)
≥5 x ULN	3/2157	(0.1)	2/2192	(0.1)	5/4349	(0.1)
≥10 x ULN	0/2157	(0.0)	1/2192	(0.0)	1/4349	(0.0)
≥20 x ULN	0/2157	(0.0)	0/2192	(0.0)	0/4349	(0.0)
Aminotransferase (ALT or AST)						
≥3 x ULN	17/2157	(0.8)	24/2192	(1.1)	41/4349	(0.9)
≥5 x ULN	6/2157	(0.3)	8/2192	(0.4)	14/4349	(0.3)
≥10 x ULN	2/2157	(0.1)	1/2192	(0.0)	3/4349	(0.1)
≥20 x ULN	1/2157	(0.0)	1/2192	(0.0)	2/4349	(0.0)
Bilirubin						
≥2 x ULN	70/2159	(3.2)	75/2193	(3.4)	145/4352	(3.3)
Alkaline Phosphatase						
≥1.5 x ULN	174/2156	(8.1)	181/2192	(8.3)	355/4348	(8.2)

Criteria	Vericiguat		Placebo		Total	
	n/m	(%)	n/m	(%)	n/m	(%)
Aminotransferase (ALT or AST) and Bilirubin						
AT ≥3 x ULN and BILI ≥1.5 x ULN	8/2159	(0.4)	6/2193	(0.3)	14/4352	(0.3)
AT ≥3 x ULN and BILI ≥2 x ULN	4/2159	(0.2)	2/2193	(0.1)	6/4352	(0.1)
Aminotransferase (ALT or AST) and Bilirubin and Alkaline Phosphatase						
AT ≥3 x ULN and BILI ≥2 x ULN and ALP <2 x ULN	3/2159	(0.1)	1/2193	(0.0)	4/4352	(0.1)

n = Number of Subjects with postbaseline test results (or combination of test results from the same day) that met predetermined criteria.
m = Number of Subjects with at least one postbaseline test result or combination of test results from the same day.
ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; AT = Aminotransferase (ALT or AST); BILI = Bilirubin; ULN = Upper limit of normal range.
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 completion date (18Jun2019).

Source: [P001MK1242: adam-adsl; addili]

Vital signs

Blood pressure

The mean reduction in systolic blood pressure was approximately 1 to 2 mm Hg greater in subjects who received vericiguat compared with placebo. No exposure-response relationship was observed between C_{max} and change of SBP from baseline from the Day 14 visit through the duration of the study.

Heart rate

No notable differences were observed between the vericiguat and placebo treatment groups in change from baseline in pulse rate.

Safety in special populations

Elderly

No dosage adjustment of vericiguat is recommended in geriatric patients. In VICTORIA, a total of 1,596 (63%) subjects treated with vericiguat were 65 years and older, and 783 (31%) subjects treated with vericiguat were 75 years and older. A slightly higher incidence in AEs was observed in patients aged ≥65 years or ≥ 75 years compared to younger patients; however, no pattern indicative for a safety signal across the subgroups could be observed (**Table 44** and **Table 45**).

Table 26. Subjects displaying adverse events in various categories

MedDRA Terms (EMA Template)	Age <65 Number of subjects (%)		Age 65 to 74 Number of subjects (%)		Age 75 to 84 Number of subjects (%)		Age 85+ Number of subjects (%)	
	Vericiguat N=923 (100)	Placebo N=943 (100)	Vericiguat N=813 (100)	Placebo N=791 (100)	Vericiguat N=634 (100)	Placebo N=647 (100)	Vericiguat N=149 (100)	Placebo N-134 (100)
Total AEs	737 (79.8)	745 (79.0)	639 (78.6)	629(79.5)	526 (83.0)	556 (85.9)	125 (83.9)	106 (79.1)
Serious AEs – Total	266 (28.8)	286 (30.3)	270 (33.2)	279 (35.3)	233 (36.8)	263 (40.6)	57 (38.3)	48 (35.8)
Fatal	21 (2.3)	27 (2.9)	29 (3.6)	24 (3.0)	24 (3.8)	30 (4.6)	9 (6.0)	4 (3.0)
Hospitalization [a] / prolong existing hospitalization	253 (27.4)	268 (28.4)	259 (31.9)	271 (34.3)	221 (34.9)	251 (38.8)	53 (35.6)	48 (35.8)
Life-threatening	59 (6.4)	59 (6.3)	52 (6.4)	50 (6.3)	48 (7.6)	52 (8.0)	12 (8.1)	8 (6.0)
Disability [b] / incapacity	9 (1.0)	9 (1.0)	10 (1.2)	10 (1.3)	6 (0.9)	14 (2.2)	2 (1.3)	4 (3.0)
Other (medically significant)	27 (2.9)	21 (2.2)	14 (1.7)	23 (2.9)	24 (3.8)	23 (3.6%)	7 (4.7)	0
AE leading to drop-out [c]	50 (5.4)	41 (4.3)	47 (5.8)	60 (7.6)	55 (8.7)	46 (7.1%)	15 (10.1)	11 (8.2)
Psychiatric disorders [d]	38 (4.1)	45 (4.8)	27 (3.3)	41 (5.2)	35 (5.5)	40 (6.2)	8 (5.4)	14 (10.4)
Nervous system disorders [d]	181 (19.6)	163 (17.3)	129 (15.9)	127 (16.1)	130 (20.5)	133 (20.6)	27 (18.1)	17 (12.7)
Accidents and injuries [e]	13 (1.4)	14 (1.5)	12 (1.5)	24 (3.0)	20 (3.2)	16 (2.5)	6 (4.0)	3 (2.2)
Cardiac disorders [d]	234 (25.4)	245 (26.0)	194 (23.9)	212 (26.8)	128 (20.2)	162 (25.0)	27 (18.1)	26 (19.4)

Vascular disorders	211 (22.9)	172 (18.2)	174 (21.4)	163 (20.6)	135 (21.3)	147 (22.7)	33 (22.1)	29 (21.6)
Cerebrovascular disorders [f]	2 (0.2)	0	0	1 (0.1)	1 (0.2)	1 (0.2)	0	0
Infections and infestations [d]	332 (36.0)	308 (32.7)	270 (33.2)	279 (35.3)	219 (34.5)	237 (36.6)	47 (31.5)	56 (41.8)
Anticholinergic syndrome [e]	0	0	0	0	0	0	0	0
Quality of life decreased [e]	0	0	0	0	0	0	0	0
Sum of postural hypotension [e], falls [f], black outs [e], syncope, dizziness [f], ataxia [f], fractures [f]	115 (12.5)	99 (10.5)	84 (10.3)	73 (9.2)	92 (14.5)	86 (13.3)	22 (14.8)	21 (15.7)
Other AE appearing more frequently in older subjects [g]	229 (24.8)	218 (23.1)	236 (29.0)	235 (29.7)	218 (34.4)	191 (29.5)	49 (32.9)	35 (26.1)

[a] AE Term "Hospitalization" was recorded in VICTORIA study

[b] AE Term "Disability" was recorded in VICTORIA study

[c] AE leading to discontinuation of study drug - was recorded in VICTORIA study

[d] AE by System Organ Class (SOC) of the Medical Dictionary of Regulatory Activities (MedDRA)

[e] a unique AE term (accidents and injuries) and MedDRA lower level terms (LLT: postural hypotension, blackout)

[f] AE by Preferred Term (PT) under SOC of the MedDRA

Table 27. Number of subjects with other frequently occurred adverse events in older age by age group (data through primary completion, all subjects as treated)

	Age < 65		Age 65 - 74		Age 75 - 84		Age 85+	
Preferred term MedDRA version 22.0	Vericiguat N=923 (100%)	Placebo N=943 (100%)	Vericiguat N=813 (100%)	Placebo N=791 (100%)	Vericiguat N=634 (100%)	Placebo N=647 (100%)	Vericiguat N=149 (100%)	Placebo N=134 (100%)
Number (%) of subjects with at least one of the following events	229 (24.8%)	218 (23.1%)	236 (29.0%)	235 (29.7%)	218 (34.4%)	191 (29.5%)	49 (32.9%)	35 (26.1%)
Acute kidney injury	50 (5.4%)	41 (4.3%)	42 (5.2%)	42 (5.3%)	34 (5.4%)	40 (6.2%)	8 (5.4%)	4 (3.0%)
Anaemia	53 (5.7%)	37 (3.9%)	61 (7.5%)	52 (6.6%)	62 (9.8%)	44 (6.8%)	16 (10.7%)	10 (7.5%)
Chronic kidney disease	27 (2.9%)	33 (3.5%)	28 (3.4%)	34 (4.3%)	26 (4.1%)	20 (3.1%)	7 (4.7%)	3 (2.2%)
Chronic obstructive pulmonary disease	18 (2.0%)	17 (1.8%)	36 (4.4%)	21 (2.7%)	19 (3.0%)	15 (2.3%)	3 (2.0%)	5 (3.7%)
Decreased appetite	10 (1.1%)	8 (0.8%)	11 (1.4%)	12 (1.5%)	11 (1.7%)	9 (1.4%)	3 (2.0%)	2 (1.5%)
Diarrhoea	37 (4.0%)	42 (4.5%)	46 (5.7%)	36 (4.6%)	39 (6.2%)	36 (5.6%)	8 (5.4%)	10 (7.5%)
Fatigue	15 (1.6%)	14 (1.5%)	16 (2.0%)	11 (1.4%)	14 (2.2%)	15 (2.3%)	4 (2.7%)	6 (4.5%)

	Age < 65		Age 65 - 74		Age 75 - 84		Age 85+	
Preferred term MedDRA version 22.0	Vericiguat N=923 (100%)	Placebo N=943 (100%)	Vericiguat N=813 (100%)	Placebo N=791 (100%)	Vericiguat N=634 (100%)	Placebo N=647 (100%)	Vericiguat N=149 (100%)	Placebo N=134 (100%)
Hypokalaemia	30 (3.3%)	35 (3.7%)	35 (4.3%)	27 (3.4%)	24 (3.8%)	22 (3.4%)	5 (3.4%)	3 (2.2%)
Nausea	35 (3.8%)	20 (2.1%)	28 (3.4%)	27 (3.4%)	30 (4.7%)	19 (2.9%)	3 (2.0%)	1 (0.7%)
Renal failure	24 (2.6%)	20 (2.1%)	29 (3.6%)	35 (4.4%)	32 (5.0%)	27 (4.2%)	7 (4.7%)	7 (5.2%)
Renal impairment	19 (2.1%)	19 (2.0%)	27 (3.3%)	24 (3.0%)	15 (2.4%)	19 (2.9%)	6 (4.0%)	4 (3.0%)

This table includes treatment-emergent events which are defined as event that started or worsened after start of study medication until last intake of study medication plus 14 days.
Adverse events in this table is selected by following criteria:
a) Events with incidence >= 2% in >=65 age group, the incidence that is higher in >=65 age group than < 65 age group, and the incidence that is higher in Vericiguat group than in placebo group.
b) Events that are not defined as 'Psychiatric disorders', 'Nervous system disorders', 'Accidents and injuries', 'Cardiac disorders', 'Cerebrovascular disorders', 'Infections and
infestations', 'Anticholinergic syndrome', 'Quality of life decreased', 'Postural hypotension', 'Fall', 'Blackout', 'Syncope', 'Dizziness', 'Ataxia' and 'Fractur e'.
Adverse events are sorted in alphabetical order by preferred term (PT). A subject is counted only once within each preferred term.

MedDRA= Medical Dictionary of Regulatory Activities, N=Number of subjects
.

Renal impairment

The difference between the vericiguat and the placebo group with respect to drug-related adverse events, serious drug-related adverse events, and discontinuation of study drug due to an adverse event is greater in the ≤ 30 mL/min/1.73m^2 subgroup compared with the >30 - ≤ 60 mL/min/1.73m^2 and the > 60 mL/min/1.73m2 subgroups (**Table 466**).

Table 28. Adverse Experience Summary by Baseline eGFR All Subjects as Treated – VICTORIA Study

	≤30 mL/min/1.73 m^2				>30 - ≤60 mL/min/1.73 m^2				>60 mL/min/1.73 m^2			
	Vericiguat		Placebo		Vericiguat		Placebo		Vericiguat		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	259		246		1,054		1,064		1,161		1,172	
with one or more adverse events	224	(86.5)	210	(85.4)	873	(82.8)	888	(83.5)	897	(77.3)	912	(77.8)
with no adverse event	35	(13.5)	36	(14.6)	181	(17.2)	176	(16.5)	264	(22.7)	260	(22.2)
with drug-related† adverse events	51	(19.7)	29	(11.8)	152	(14.4)	136	(12.8)	157	(13.5)	121	(10.3)
with non-serious adverse events	213	(82.2)	194	(78.9)	832	(78.9)	843	(79.2)	859	(74.0)	869	(74.1)
with serious adverse events	109	(42.1)	116	(47.2)	389	(36.9)	423	(39.8)	316	(27.2)	324	(27.6)
with serious drug-related adverse events	9	(3.5)	3	(1.2)	15	(1.4)	11	(1.0)	6	(0.5)	5	(0.4)
with dose modification‡ due to an adverse event	78	(30.1)	88	(35.8)	304	(28.8)	280	(26.3)	257	(22.1)	226	(19.3)
who died§	16	(6.2)	16	(6.5)	38	(3.6)	39	(3.7)	27	(2.3)	28	(2.4)
who died due to a drug-related adverse event	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	30	(11.6)	33	(13.4)	80	(7.6)	74	(7.0)	53	(4.6)	47	(4.0)
discontinued drug due to a drug-related adverse event	14	(5.4)	6	(2.4)	29	(2.8)	21	(2.0)	20	(1.7)	18	(1.5)
discontinued drug due to a serious adverse event	13	(5.0)	22	(8.9)	40	(3.8)	38	(3.6)	17	(1.5)	25	(2.1)
discontinued drug due to a serious drug-related adverse event	3	(1.2)	1	(0.4)	8	(0.8)	3	(0.3)	2	(0.2)	4	(0.3)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
§ Includes adverse events associated with a fatal outcome but does not reflect all deaths reported in the study.
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 completion date (18Jun2019).

Source: P001MK1242: adam-adsl; adae

Hepatic impairment

Since INR or ascites data were not captured in VICTORIA, an alternative approach, the ALBI grading system, is provided, which relies on a score calculated using only albumin and bilirubin values. The incidences of any AEs as well as SAEs were comparable in the vericiguat and placebo treatment arms in subjects with ALBI grade 1 and 2 at baseline. The incidences of drug-related AEs were reported higher in the vericiguat treatment arm when compared to placebo for subjects with ALBI grade 1 (vericiguat: 14.7%, 288 cases /1963 subjects; placebo: 11.9%, 230 cases/1926 subjects) and ALBI grade 2 (vericiguat: 14.1% , 71 cases/504 subjects; placebo: 10.7%, 59 cases/552 subjects). The total number of fatal outcomes due to AEs was almost 2-fold higher in subjects with ALBI grade 2 at baseline (5.3%, 56 cases/1056 subjects in total; vericiguat: 2.6%; placebo: 2.9%) when compared with subjects with ALBI grade 1 (2.8%, 107 cases / 3889 subjects in total; vericiguat: 5.6%; placebo: 5.1); however, these incidences were comparable in both the vericiguat and placebo treatment arms

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

Organic nitrates

In VICTORIA, concomitant nitrate use was assessed at each study visit, and 11.9% of subjects reported any nitrate or NO donor use at one or more visits. Long-acting nitrates or NO donors co-administered with study medication were reported as a protocol deviation in 3.2 % of subjects. Among subjects reporting concomitant use of any nitrate and either vericiguat or placebo, 99.8% reported the

combination was well tolerated since none was not well-tolerated due to symptomatic hypotension syncope was reported in the vericiguat group who used nitrate or NO donor at one or more visits.

In subjects with heart failure, concomitant use of short-acting nitrates was well tolerated. There is limited experience with concomitant use of vericiguat and long-acting nitrates in subjects with heart failure.

PDE-5 inhibitors

In a PD interaction study, coadministration of vericiguat with sildenafil was generally well tolerated; however, the coadministration was associated with an increased frequency of transient AEs, most commonly headache and head discomfort. This interaction study was conducted in parallel to the Phase 3 study; therefore, the use of PDE 5 inhibitors was prohibited in VICTORIA. Unintentional coadministration in VICTORIA was very rare (only 2 subjects received vericiguat and a PDE 5 inhibitor concomitantly). Concomitant use of vericiguat and PDE-5 inhibitors, such as sildenafil, has not been studied in patients with heart failure and is therefore not recommended due to the potential increased risk for symptomatic hypotension.

Other soluble guanylate cyclase stimulators

Coadministration of vericiguat and other sGC stimulators was not permitted in VICTORIA. Therefore, vericiguat is contraindicated in patients with concomitant use of other sGC stimulators, such as riociguat.

Discontinuation due to adverse events

The proportion of subjects who discontinued study medication due to an AE was slightly higher in the vericiguat group compared with the placebo group (6.6% versus 6.3%, respectively) (**Table 47**). The most common AE that led to discontinuation was hypotension, which led to study medication discontinuation in 1.9% of subjects in the vericiguat group and 1.3% of subjects in the placebo group.

In SOCRATES-REDUCED the most frequently reported TEAEs (incidence ≥2%) resulting in study medication discontinuation were cardiac failure, metabolic acidosis, acute kidney injury, and rash.

Table 29. Subjects With Adverse Events Leading to Treatment Discontinuation (Incidence > 0% in One or More Treatment Groups) All Subjects as Treated

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	2,519		2,515		5,034	
with one or more adverse events leading to treatment discontinuation	167	(6.6)	158	(6.3)	325	(6.5)
with no adverse events leading to treatment discontinuation	2,352	(93.4)	2,357	(93.7)	4,709	(93.5)
Blood and lymphatic system disorders	**3**	**(0.1)**	**0**	**(0.0)**	**3**	**(0.1)**
Anaemia	2	(0.1)	0	(0.0)	2	(0.0)
Pancytopenia	1	(0.0)	0	(0.0)	1	(0.0)
Cardiac disorders	**8**	**(0.3)**	**13**	**(0.5)**	**21**	**(0.4)**
Angina pectoris	1	(0.0)	1	(0.0)	2	(0.0)
Aortic valve calcification	1	(0.0)	0	(0.0)	1	(0.0)
Aortic valve stenosis	0	(0.0)	1	(0.0)	1	(0.0)
Cardiac arrest	1	(0.0)	0	(0.0)	1	(0.0)
Cardiac failure	4	(0.2)	5	(0.2)	9	(0.2)
Cardiac failure acute	0	(0.0)	1	(0.0)	1	(0.0)
Cardiac failure chronic	0	(0.0)	2	(0.1)	2	(0.0)
Cardiac failure congestive	0	(0.0)	1	(0.0)	1	(0.0)
Cardio-respiratory arrest	0	(0.0)	1	(0.0)	1	(0.0)
Cardiogenic shock	0	(0.0)	1	(0.0)	1	(0.0)
Ventricular tachycardia	1	(0.0)	1	(0.0)	2	(0.0)
Ear and labyrinth disorders	**2**	**(0.1)**	**2**	**(0.1)**	**4**	**(0.1)**
Vertigo	2	(0.1)	2	(0.1)	4	(0.1)
Endocrine disorders	**1**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**
Carcinoid syndrome	1	(0.0)	0	(0.0)	1	(0.0)
Eye disorders	**1**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**
Diplopia	1	(0.0)	0	(0.0)	1	(0.0)
Gastrointestinal disorders	**18**	**(0.7)**	**17**	**(0.7)**	**35**	**(0.7)**
Abdominal discomfort	1	(0.0)	0	(0.0)	1	(0.0)
Abdominal distension	1	(0.0)	0	(0.0)	1	(0.0)
Abdominal pain	1	(0.0)	1	(0.0)	2	(0.0)
Abdominal pain upper	0	(0.0)	1	(0.0)	1	(0.0)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**18**	**(0.7)**	**17**	**(0.7)**	**35**	**(0.7)**
Ascites	1	(0.0)	0	(0.0)	1	(0.0)
Constipation	0	(0.0)	1	(0.0)	1	(0.0)
Diarrhoea	2	(0.1)	3	(0.1)	5	(0.1)
Dyspepsia	4	(0.2)	2	(0.1)	6	(0.1)
Faecaloma	0	(0.0)	1	(0.0)	1	(0.0)
Faeces discoloured	1	(0.0)	0	(0.0)	1	(0.0)
Gastritis	0	(0.0)	2	(0.1)	2	(0.0)
Gastrointestinal angiodysplasia	0	(0.0)	1	(0.0)	1	(0.0)
Gastrointestinal haemorrhage	0	(0.0)	1	(0.0)	1	(0.0)
Gastrooesophageal reflux disease	1	(0.0)	0	(0.0)	1	(0.0)
Melaena	1	(0.0)	0	(0.0)	1	(0.0)
Nausea	6	(0.2)	1	(0.0)	7	(0.1)
Odynophagia	1	(0.0)	0	(0.0)	1	(0.0)
Oesophageal achalasia	0	(0.0)	1	(0.0)	1	(0.0)
Oesophageal varices haemorrhage	0	(0.0)	1	(0.0)	1	(0.0)
Pancreatolithiasis	1	(0.0)	0	(0.0)	1	(0.0)
Peptic ulcer	0	(0.0)	1	(0.0)	1	(0.0)
Vomiting	1	(0.0)	0	(0.0)	1	(0.0)
General disorders and administration site conditions	**8**	**(0.3)**	**5**	**(0.2)**	**13**	**(0.3)**
Asthenia	3	(0.1)	1	(0.0)	4	(0.1)
Chest discomfort	0	(0.0)	1	(0.0)	1	(0.0)
Chest pain	1	(0.0)	1	(0.0)	2	(0.0)
Fatigue	2	(0.1)	1	(0.0)	3	(0.1)
General physical health deterioration	2	(0.1)	1	(0.0)	3	(0.1)
Hepatobiliary disorders	**4**	**(0.2)**	**2**	**(0.1)**	**6**	**(0.1)**
Hepatic congestion	1	(0.0)	0	(0.0)	1	(0.0)
Hepatic function abnormal	0	(0.0)	1	(0.0)	1	(0.0)
Hyperbilirubinaemia	0	(0.0)	1	(0.0)	1	(0.0)
Ischaemic hepatitis	1	(0.0)	0	(0.0)	1	(0.0)
Liver disorder	1	(0.0)	0	(0.0)	1	(0.0)
Liver injury	1	(0.0)	0	(0.0)	1	(0.0)
Immune system disorders	**4**	**(0.2)**	**0**	**(0.0)**	**4**	**(0.1)**

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Immune system disorders	**4**	**(0.2)**	**0**	**(0.0)**	**4**	**(0.1)**
Amyloidosis	1	(0.0)	0	(0.0)	1	(0.0)
Hypersensitivity	2	(0.1)	0	(0.0)	2	(0.0)
Seasonal allergy	1	(0.0)	0	(0.0)	1	(0.0)
Infections and infestations	**7**	**(0.3)**	**15**	**(0.6)**	**22**	**(0.4)**
Cellulitis	0	(0.0)	2	(0.1)	2	(0.0)
Device related infection	0	(0.0)	1	(0.0)	1	(0.0)
Disseminated tuberculosis	0	(0.0)	1	(0.0)	1	(0.0)
Gastroenteritis	0	(0.0)	1	(0.0)	1	(0.0)
Intervertebral discitis	1	(0.0)	0	(0.0)	1	(0.0)
Necrotising fasciitis	1	(0.0)	0	(0.0)	1	(0.0)
Pneumonia	3	(0.1)	5	(0.2)	8	(0.2)
Pneumonia bacterial	0	(0.0)	1	(0.0)	1	(0.0)
Respiratory tract infection	1	(0.0)	0	(0.0)	1	(0.0)
Salmonella bacteraemia	0	(0.0)	1	(0.0)	1	(0.0)
Sepsis	1	(0.0)	0	(0.0)	1	(0.0)
Septic shock	0	(0.0)	1	(0.0)	1	(0.0)
Upper respiratory tract infection	0	(0.0)	1	(0.0)	1	(0.0)
Urinary tract infection	0	(0.0)	1	(0.0)	1	(0.0)
Injury, poisoning and procedural complications	**5**	**(0.2)**	**4**	**(0.2)**	**9**	**(0.2)**
Asbestosis	1	(0.0)	0	(0.0)	1	(0.0)
Cervical vertebral fracture	1	(0.0)	0	(0.0)	1	(0.0)
Fall	0	(0.0)	1	(0.0)	1	(0.0)
Femoral neck fracture	0	(0.0)	2	(0.1)	2	(0.0)
Femur fracture	1	(0.0)	0	(0.0)	1	(0.0)
Intentional overdose	1	(0.0)	0	(0.0)	1	(0.0)
Limb injury	1	(0.0)	0	(0.0)	1	(0.0)
Rib fracture	0	(0.0)	1	(0.0)	1	(0.0)
Subdural haematoma	0	(0.0)	1	(0.0)	1	(0.0)
Thermal burn	0	(0.0)	1	(0.0)	1	(0.0)
Wound secretion	0	(0.0)	1	(0.0)	1	(0.0)
Investigations	**9**	**(0.4)**	**4**	**(0.2)**	**13**	**(0.3)**
Blood creatinine increased	4	(0.2)	1	(0.0)	5	(0.1)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Investigations	**9**	**(0.4)**	**4**	**(0.2)**	**13**	**(0.3)**
Cardiac index abnormal	1	(0.0)	0	(0.0)	1	(0.0)
Gamma-glutamyltransferase increased	1	(0.0)	1	(0.0)	2	(0.0)
Hepatic enzyme increased	2	(0.1)	0	(0.0)	2	(0.0)
Liver function test increased	0	(0.0)	1	(0.0)	1	(0.0)
Platelet count decreased	1	(0.0)	0	(0.0)	1	(0.0)
Weight increased	0	(0.0)	1	(0.0)	1	(0.0)
Metabolism and nutrition disorders	**6**	**(0.2)**	**7**	**(0.3)**	**13**	**(0.3)**
Appetite disorder	1	(0.0)	0	(0.0)	1	(0.0)
Decreased appetite	2	(0.1)	0	(0.0)	2	(0.0)
Dehydration	0	(0.0)	1	(0.0)	1	(0.0)
Fluid overload	0	(0.0)	1	(0.0)	1	(0.0)
Gout	1	(0.0)	1	(0.0)	2	(0.0)
Hypercalcaemia	0	(0.0)	1	(0.0)	1	(0.0)
Hyperkalaemia	0	(0.0)	2	(0.1)	2	(0.0)
Hyponatraemia	0	(0.0)	1	(0.0)	1	(0.0)
Ketoacidosis	0	(0.0)	1	(0.0)	1	(0.0)
Marasmus	1	(0.0)	0	(0.0)	1	(0.0)
Metabolic acidosis	1	(0.0)	1	(0.0)	2	(0.0)
Musculoskeletal and connective tissue disorders	**2**	**(0.1)**	**1**	**(0.0)**	**3**	**(0.1)**
Haematoma muscle	0	(0.0)	1	(0.0)	1	(0.0)
Myalgia	1	(0.0)	0	(0.0)	1	(0.0)
Sjogren's syndrome	1	(0.0)	0	(0.0)	1	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**5**	**(0.2)**	**8**	**(0.3)**	**13**	**(0.3)**
Breast cancer	0	(0.0)	1	(0.0)	1	(0.0)
Bronchial carcinoma	1	(0.0)	0	(0.0)	1	(0.0)
Diffuse large B-cell lymphoma	0	(0.0)	1	(0.0)	1	(0.0)
Hepatic cancer metastatic	0	(0.0)	1	(0.0)	1	(0.0)
Hepatic neoplasm	0	(0.0)	1	(0.0)	1	(0.0)
Lung cancer metastatic	1	(0.0)	0	(0.0)	1	(0.0)
Lung neoplasm malignant	0	(0.0)	2	(0.1)	2	(0.0)
Metastases to lymph nodes	0	(0.0)	1	(0.0)	1	(0.0)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**5**	**(0.2)**	**8**	**(0.3)**	**13**	**(0.3)**
Oesophageal carcinoma	1	(0.0)	0	(0.0)	1	(0.0)
Pancreatic carcinoma	0	(0.0)	1	(0.0)	1	(0.0)
Pancreatic carcinoma metastatic	1	(0.0)	0	(0.0)	1	(0.0)
Plasmacytoma	0	(0.0)	1	(0.0)	1	(0.0)
Squamous cell carcinoma of head and neck	1	(0.0)	0	(0.0)	1	(0.0)
Nervous system disorders	**18**	**(0.7)**	**18**	**(0.7)**	**36**	**(0.7)**
Axonal neuropathy	1	(0.0)	0	(0.0)	1	(0.0)
Brain injury	2	(0.1)	0	(0.0)	2	(0.0)
Cerebrovascular accident	0	(0.0)	1	(0.0)	1	(0.0)
Cognitive disorder	0	(0.0)	1	(0.0)	1	(0.0)
Coma	1	(0.0)	0	(0.0)	1	(0.0)
Dementia	1	(0.0)	0	(0.0)	1	(0.0)
Dizziness	9	(0.4)	3	(0.1)	12	(0.2)
Dysarthria	0	(0.0)	1	(0.0)	1	(0.0)
Dysgeusia	1	(0.0)	0	(0.0)	1	(0.0)
Dyskinesia	0	(0.0)	1	(0.0)	1	(0.0)
Generalised tonic-clonic seizure	0	(0.0)	1	(0.0)	1	(0.0)
Headache	0	(0.0)	1	(0.0)	1	(0.0)
Hypoxic-ischaemic encephalopathy	1	(0.0)	1	(0.0)	2	(0.0)
Ischaemic stroke	1	(0.0)	0	(0.0)	1	(0.0)
Metabolic encephalopathy	0	(0.0)	1	(0.0)	1	(0.0)
Somnolence	0	(0.0)	1	(0.0)	1	(0.0)
Syncope	1	(0.0)	6	(0.2)	7	(0.1)
Psychiatric disorders	**2**	**(0.1)**	**4**	**(0.2)**	**6**	**(0.1)**
Depressed mood	0	(0.0)	1	(0.0)	1	(0.0)
Drug use disorder	1	(0.0)	0	(0.0)	1	(0.0)
Mental status changes	0	(0.0)	1	(0.0)	1	(0.0)
Restlessness	0	(0.0)	1	(0.0)	1	(0.0)
Sleep disorder	0	(0.0)	1	(0.0)	1	(0.0)
Suicide attempt	1	(0.0)	0	(0.0)	1	(0.0)
Renal and urinary disorders	**25**	**(1.0)**	**37**	**(1.5)**	**62**	**(1.2)**

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Renal and urinary disorders	**25**	**(1.0)**	**37**	**(1.5)**	**62**	**(1.2)**
Acute kidney injury	10	(0.4)	10	(0.4)	20	(0.4)
Chronic kidney disease	8	(0.3)	14	(0.6)	22	(0.4)
Haematuria	1	(0.0)	0	(0.0)	1	(0.0)
Nephropathy	1	(0.0)	0	(0.0)	1	(0.0)
Renal cyst	0	(0.0)	1	(0.0)	1	(0.0)
Renal failure	4	(0.2)	10	(0.4)	14	(0.3)
Renal impairment	1	(0.0)	2	(0.1)	3	(0.1)
Reproductive system and breast disorders	**1**	**(0.0)**	**2**	**(0.1)**	**3**	**(0.1)**
Erectile dysfunction	0	(0.0)	1	(0.0)	1	(0.0)
Erection increased	1	(0.0)	0	(0.0)	1	(0.0)
Gynaecomastia	0	(0.0)	1	(0.0)	1	(0.0)
Respiratory, thoracic and mediastinal disorders	**6**	**(0.2)**	**6**	**(0.2)**	**12**	**(0.2)**
Acute pulmonary oedema	1	(0.0)	0	(0.0)	1	(0.0)
Acute respiratory failure	1	(0.0)	1	(0.0)	2	(0.0)
Chronic obstructive pulmonary disease	1	(0.0)	1	(0.0)	2	(0.0)
Dyspnoea	1	(0.0)	0	(0.0)	1	(0.0)
Haemoptysis	1	(0.0)	0	(0.0)	1	(0.0)
Interstitial lung disease	0	(0.0)	1	(0.0)	1	(0.0)
Nasal congestion	0	(0.0)	1	(0.0)	1	(0.0)
Pleural effusion	0	(0.0)	1	(0.0)	1	(0.0)
Productive cough	0	(0.0)	1	(0.0)	1	(0.0)
Pulmonary hypertension	1	(0.0)	1	(0.0)	2	(0.0)
Skin and subcutaneous tissue disorders	**6**	**(0.2)**	**7**	**(0.3)**	**13**	**(0.3)**
Angioedema	0	(0.0)	1	(0.0)	1	(0.0)
Dermatitis bullous	0	(0.0)	1	(0.0)	1	(0.0)
Henoch-Schonlein purpura	0	(0.0)	1	(0.0)	1	(0.0)
Pruritus	3	(0.1)	1	(0.0)	4	(0.1)
Psoriasis	1	(0.0)	0	(0.0)	1	(0.0)
Rash	2	(0.1)	1	(0.0)	3	(0.1)
Rash generalised	0	(0.0)	1	(0.0)	1	(0.0)
Rash pruritic	1	(0.0)	0	(0.0)	1	(0.0)

	Vericiguat		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**6**	**(0.2)**	**7**	**(0.3)**	**13**	**(0.3)**
Urticaria	0	(0.0)	1	(0.0)	1	(0.0)
Surgical and medical procedures	**1**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**
Cardioversion	1	(0.0)	0	(0.0)	1	(0.0)
Vascular disorders	**49**	**(1.9)**	**36**	**(1.4)**	**85**	**(1.7)**
Bleeding varicose vein	1	(0.0)	0	(0.0)	1	(0.0)
Circulatory collapse	0	(0.0)	1	(0.0)	1	(0.0)
Haematoma	1	(0.0)	0	(0.0)	1	(0.0)
Hypertension	0	(0.0)	1	(0.0)	1	(0.0)
Hypotension	47	(1.9)	32	(1.3)	79	(1.6)
Orthostatic hypotension	1	(0.0)	0	(0.0)	1	(0.0)
Shock haemorrhagic	0	(0.0)	1	(0.0)	1	(0.0)
Vasculitis	0	(0.0)	1	(0.0)	1	(0.0)

Every subject is counted a single time for each applicable row and column.
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 completion date (18Jun2019).

Source: [P001MK1242: adam-adsl; adae]

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

Like riociguat, vericiguat belongs to the pharmacological class, soluble cyclase stimulators, so there is previous safety experience with medicinal product belonging to the same pharmacological class. In the current dossier, the primary safety data are derived from the pivotal study VICTORIA, supplemented by phase 1 and phase 2 studies, particularly the phase 2 study SOCRATES-REDUCED when applicable.

Patient exposure. In VICTORIA, a total of 2519 subjects with heart failure with reduced ejection fraction (HFrEF) has been exposed to any vericiguat dose and 2063 subjects with HFrEH to 10 mg vericiguat (mean duration of 375.5 days and 362.0 days, respectively). Further, a number of 1154 subjects with HFrEF was exposed to vericiguat for at least one year. In SOCRATES-REDUCED, a total of 363 subjects with HFrEF has been exposed to any dose vericiguat, with a mean duration of 73.4 days. Overall, the documented safety exposure exceeds the requirements of ICH-E1 and is considered sufficient for adequate assessment of the safety profile of vericiguat.

Adverse events. In VICTORIA, TEAEs were frequently reported; however, the percentage of subjects with one or more adverse events was similar between the vericiguat (80.5%) and placebo (81.0%) group. The system organ classes mostly affected and with a higher rate of reported adverse events in the vericiguat group were "gastrointestinal disorders" (25.3% versus 21.7% in placebo), "vascular disorders" (22.0% versus 20.3%), "nervous system disorders" (18.5% versus 17.55), and "blood and lymphatic system disorders" (10.6% versus 8.4%). The most frequent AEs with a higher incidence with vericiguat compared with placebo were hypotension (15.4% versus 14.1), anaemia (7.6% versus 5.7%), dyspepsia (2.7% versus 1.1%), nausea (3.8% versus 2.7%), and headache (3.4% versus 2.4%), which is in line with the mechanism of action and in line with riociguat, another sGC stimulator. The incidence of AEs considered related to study drug was slightly higher in the vericiguat group

(14.6%) compared with the placebo group (11.7%). The most frequent drug-related AEs with a higher incidence in vericiguat compared with placebo (≥ 0.3% difference) were hypotension (6.8% [n=172] and 5.9% [n=149], dizziness (1.5% [n=37] and 0.9% [n=22], nausea (0.8% [n=19] and 0.2% [n=5], orthostatic hypotension (0.6% [n=14] and 0.3% [n=8], dyspepsia (0.6% [n=14] and 0.3% [n=8]), gastroesophageal reflux disease (0.4% [n=9] and 0% [n=0]).

AEs of special interest. *Hypotension*. In VICTORIA, hypotension was more frequently reported in the vericiguat group than the placebo group (15.4 % and 14.1%, respectively). Comparable results were observed for orthostatic hypotension (1.3% versus 1.0%) and symptomatic hypotension (9.1% versus 7.9%). The percentage of subjects with serious adverse events was 1.3% in the vericiguat group and 1.7% in placebo group for hypotension, 0.2% (n=6) and 0% (n=1) for orthostatic hypotension, and 1.2% and 1.5% for symptomatic. Serious drug-related adverse events were low (0.4% of the subjects in each group for hypotension and only one event of orthostatic hypotension in the placebo group), which is reassuring. A slightly higher percentage of patients treated with vericiguat compared with placebo experienced an adverse event of hypotension at the 2.5 mg and 5 mg dose, whereas the percentage of patients with hypotension was generally comparable between vericiguat and placebo at the 10 mg target dose. These findings suggest that the differences in hypotension event rate between vericiguat and placebo occurred early persisted throughout the study, indicating that the risk of (symptomatic or orthostatic) hypotension can be adequately managed by careful clinical monitoring. Consistent results with respect to slightly higher incidences in symptomatic hypotension could be observed in the subgroup analyses with respect to NYHA class and use of sacubitril/valsartan. The subgroup analyses of CCSA showed inconsistent results, probably due to the limited number of subjects with angina. Furthermore, patients above 75 years of age, patients with moderate renal impairment, patients not using MRAs at baseline, and patients with systolic BP at baseline of < median were not more vulnerable to the hypotensive effect of vericiguat.

Syncope. In VICTORIA, the percentages of subjects with a syncope AE and SAE were slightly higher in the vericiguat group compared with placebo (4.0% versus 3.5% and 1.7% versus 1.3%, respectively). However, the percentages in drug-related syncope AE and SAE were similar between the vericiguat and placebo group (0.3% versus 0.4% and 0.1% in each group, respectively), which is reassuring.

Hepatic events. Vericiguat does not seem to affect hepatic function. Although the percentage hepatic AEs and hepatic SAEs were slightly higher in the vericiguat group compared with the placebo group (0.9% versus 0.5% and 0.6% versus 0.3%, respectively), the event rate was low, and no specific pattern in the type of hepatic event could be observed. Additionally, none of the hepatic events was considered drug-related. Moreover, the proportions of subjects with elevations in ALT/ AST with or without bilirubin elevations and alkaline phosphatase were similar between both treatment groups.

Anaemia. There is a slightly higher incidence of anaemia reported with vericiguat compared with placebo (7.6% versus 5.7%, respectively). Similarly, the percentage of subjects with serious adverse events of anaemia was low, but also slightly higher in the vericiguat group compared with the placebo group (1.6% versus 0.9%). The effect on anaemia is reflected in the proportion of subjects with a decrease in hematocrit of 10 percentage points with a value that was below the lower limit of normal, which was higher in the vericiguat group (3.9%) compared with the placebo group (2.2%). Similar findings were noted for subjects with a decrease in haemoglobin ≥3 g/dL with a value below the lower limit of normal (5.0% in the vericiguat group compared with 3.2% in the placebo group). Although none of the (serious) events of anaemia in the vericiguat group was considered treatment-related, anaemia is reported as an adverse reaction in section 4.8 of the SmPC, which is in line with the SmPC of riociguat.

GI disorders. There is a higher incidence of GI-related AEs reported in the vericiguat group (25.3%) compared with the placebo group (21.7%). The percentage of subjects with drug-related adverse

events of these specific AEs were 0.3% versus 0.2 % for diarrhoea, 0.8% versus 0.2% for nausea, 0.6% versus 0.3% for dyspepsia, 0.1% versus 0.2% for vomiting, and 0.4% versus 0% for gastroesophageal reflux disease. Furthermore, none of these types of GI events was considered drug-related by the investigator. In addition, GI disorders are also described with other vasodilators, e.g. riociguat, PDE5 inhibitors.

Acute renal injury. In VICTORIA, the incidence of acute kidney injury was approximately similar between the vericiguat group and the placebo group (5.3% (n=134) versus 5.0% (n=127), respectively). Acute kidney injury considered related by study drug was reported in 8 subjects (0.3%) in the vericiguat group and 6 subjects (0.2%) in the placebo group.

Bone disorders. It is generally accepted that the NO-sGC-cGMP and the natriuretic peptide- particulate (membrane-bound) guanylate cyclase (pGC)-cGMP pathway play an important role in the regulation of bone and cartilage homeostasis, and the stimulation of these pathways results in activation of bone formation rather than in bone resorption. For clinical evaluation on the potency of vericiguat to influence bone metabolism, reference is made to data with riociguat. A mechanistic study with riociguat performed with healthy male volunteers did not indicate a risk for riociguat-related effects on bone metabolism. Furthermore, post-marketing safety data with riociguat gave no evidence for an increased risk of adverse events on the bone. Moreover, although limited, safety data of the main part of a 6 months open-label uncontrolled study with the sGC stimulator riociguat in children aged 6 to <18 years with PAH (PATENT-CHILD), did not show bone and/or growth anomalies in this population.

Serious AEs. The incidence of SAE was relatively high; however, a slightly lower percentage of subjects in the vericiguat group experienced SAE compared with the placebo group (32.8% versus 34.8%). The incidence in serious drug-related adverse events was slightly higher in the vericiguat group compared with the placebo group (1.2% versus 0.8%); however, no pattern indicative for a safety signal could be identified among the types of drug-related serious adverse events, which is reassuring.

Deaths. All-cause mortality was lower for vericiguat compared with placebo. This result was driven by CV death and is covered in the efficacy section.

Laboratory findings. *Haematology* discussed under anaemia. *Clinical chemistry* discussed under acute renal injury or hepatic events.

Vital signs. Consistent with the findings on hypotension, the mean reduction in systolic blood pressure was approximately 1 to 2 mm Hg greater in subjects who received vericiguat compared with placebo.

Safety in special populations.

*Elderly***.** Patients of ≥65 and ≥ 75 years of age are adequately represented in VICTORIA (63% and 31%, respectively). Although slightly higher adverse event rates could be observed with advancing age, no specific pattern indicative for a safety signal across the subgroups could be observed, except for anaemia. Older patients (age ≥ 75) appears slightly more vulnerable to anaemia than younger patients (age < 75), irrespective of the treatment.

Renal impairment. Patients with renal impairment were adequately represented in VICTORIA. The difference between the vericiguat and the placebo group with respect to drug-related adverse events, serious drug-related adverse events, and discontinuation of study drug due to an adverse event is greater in the ≤ 30 mL/min/1.73m^2 subgroup compared with the >30 - ≤ 60 mL/min/1.73m^2 and the > 60 mL/min/1.73m^2 subgroups; however, no specific pattern in the type of (serious) drug-related adverse events or type of AE leading to discontinuation indicative for a safety signal could be observed, which the exception of renal and urinary disorders. The Applicant's evaluation of each drug-related event of acute kidney injury or chronic kidney disease, supplemented with the patient narratives

showed that concomitant diseases, medications or other events constitute more plausible alternative explanations for the observed differences in events. As such it is concluded that patients with severe (eGFR ≤ 30 mL / min / 1.73 m2) or moderate (eGFR > 30 to ≤ 60 mL/min/1.73 m2) renal impairment are not more vulnerable to renal and urinary disorders, i.e. acute kidney injury or chronic kidney disease, upon treatment with vericiguat.

Hepatic impairment. In VICTORIA, subjects with mild and moderate hepatic impairment were allowed to be enrolled. No differences in safety profiles between the ALBI score grades 1 and 2 has been identified.

Safety related to drug-drug interactions and other interactions. Discussed under pharmacodynamics.

Discontinuations due to AEs. The incidence of AEs leading to discontinuations was slightly higher in the vericiguat group compared with the placebo group (6.6% versus 6.3%). The most frequent AEs leading to discontinuations with a higher incidence in the vericiguat group compared with the placebo group were hypotension (1.9% versus 1.3%), dyspepsia (0.2% versus 0.1%), and nausea (0.2% and 0.0%), which is in line with the mechanism of action. Nevertheless, the incidences in these AEs leading to discontinuations were low, which is reassuring.

The safety results of SOCRATES-REDUCED were consistent with the findings in VICTORIA.

2.6.2. Conclusions on the clinical safety

Vericiguat belongs to the pharmacological class: soluble cyclase stimulators like riociugat. Generally, the safety profile of vericiguat is in line with riociguat and reflects its mechanism of action as a vasodilator with the following most often observed adverse events: hypotension, dizziness, nausea and gastrointestinal (GI) disorders. The application was considered approvable from clinical safety point of view.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use in patients with severe renal impairment (eGFR <15 mL/min/1.73 m^2) Use in patients with severe hepatic impairment

Pharmacovigilance plan

Routine pharmacovigilance is considered sufficient to further characterise the safety concerns of the product.

Risk minimisation measures

Safety concern	Risk minimisation measures
Use in patients with severe renal impairment (eGFR <15 mL/min/1.73 m^2) (Missing information)	Routine risk communication: • SmPC sections 4.2 and 5.2. Routine risk communication recommending specific clinical measure to address the risk: • Treatment with vericiguat is not recommended in patients with eGFR <15 mL/min/1.73 m^2 at treatment initiation or on dialysis (SmPC Section 4.4) Other routine risk minimisation measures beyond the Product Information: • Prescription-only medicine Additional risk minimisation measures: None
Use in patients with severe hepatic impairment (Missing information)	Routine risk communication: • SmPC sections 4.2 and 5.2 Routine risk communication recommending specific clinical measure to address the risk: • Treatment with vericiguat is not recommended in patients with severe hepatic impairment (SmPC Section 4.4) Other routine risk minimisation measures beyond the Product Information: • Prescription-only medicine Additional risk minimisation measures: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 19 Jan 2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of vericiguat with active substances contained in authorised medicinal products in the European Union and demonstrated that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers vericiguat to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Verquvo (vericiguat) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Vericiguat is proposed to be indicated for the treatment of symptomatic chronic heart failure (HF) in adult patients with reduced ejection fraction (HFrEF) who are stabilised after a recent decompensation event requiring intravenous therapy. Heart failure is a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection. The most important causal risk factors for HF are coronary heart disease and hypertension (systolic blood pressure [SBP] >140 mmHg). Together, these factors account for approximately half of new-onset HF cases. Furthermore, among modifiable lifestyle factors, there is an association between the onset of HF and being overweight, smoking, sedentarism, and dietary factors. Heart failure is a progressive disease associated with a high mortality rate, frequent hospitalizations and poor quality of life. Across Europe, fifteen million individuals have been reported to have HF (Benjamin et al. 2019, Dickstein et al., 2008).

The main therapeutic goals in the treatment of chronic HF is to reduce mortality and HF hospitalization.

3.1.2. Available therapies and unmet medical need

Current treatments for chronic HFrEF were established based on large randomized, controlled trials, with the results incorporated into guidelines issued by the ACCF/AHA and the European Society of Cardiology. The current standard of care of pharmacologic treatment for heart failure with reduced ejection fraction (HFrEF) includes angiotensin-converting enzyme (ACE) inhibitors (ACEis) as the cornerstone of the renin-angiotensin system (RAS)-based therapy in conjunction with β-blockers and/or mineralocorticoid antagonists (MRAs) as tolerated by the patient (Heart Failure Society of America 2010, McMurray et al. 2012, Yancy et al. 2013). Angiotensin receptor blocker (ARBs) have not been consistently proven to reduce mortality in patients with HFrEF, and their use should be restricted to patients intolerant of an ACEI or those who take an ACEI but are unable to tolerate an MRAs. Angiotensin receptor / neprilysin inhibitors (ARNI; valsartan/sacubitril) are recommended to replace ACEIs in ambulatory HFrEF patients who remain symptomatic despite optimal therapy.

Despite medical advances in the treatment of chronic HFrEF over the last 2 decades, patients continue to experience worsening HF events. Data from two retrospective studies analyzing insurance claims in the US reveal that up to 33% of HFrEF patients experience a worsening event (defined as HF hospitalization or IV diuretic use) within 12 months of the initial claim (Butler et al. 2020b, Mentz et al. 2020). Of the more than 5000 HFrEF patients enrolled in the European Society of Cardiology Heart Failure Long-term Registry, outcomes at 1 year indicated that 8.8% of patients had died, 31.9% were hospitalized for any reason, 14.6% were hospitalized for HF, and 21.2% were hospitalized for HF or died (Chioncel et al. 2017). Therefore, there is a high unmet medical need for new therapies with different mechanisms of action for HF treatment that can provide a further reduction in mortality and morbidity and improvement in the quality of life as compared to the current standard of care.

3.1.3. Main clinical studies

The main evidence of efficacy submitted (VICTORIA) is a single-phase 3 randomized, parallel-group, placebo-controlled, double-blind, event-driven, multicentre clinical outcome trial evaluating the efficacy and safety of vericiguat, when added to background standard of care, in subjects with worsening HFrEF

defined as HF hospitalization within 6 months prior to randomization or use of IV diuretics for HF [without hospitalization] within 3 months prior to randomization. Further subjects were required to have left ventricular ejection fraction (LVEF) < 45%, elevated levels of natriuretic peptides (NT-proBNP ≥1000 pg/mL or BNP ≥300 pg/mL in sinus rhythm or NT-proBNP ≥1600 pg/mL or BNP ≥500 pg/mL in atrial fibrillation), and be clinically stable at the time of randomization. Patients with SBP < 100 mmHg or symptomatic hypotension, concurrent use of long-acting nitrates or nitric oxide donors, PDE5 inhibitors, or sGC stimulators were excluded. The study included 2 treatment groups (vericiguat and placebo, 1:1 randomization) and used a titration regimen started with 2.5 mg vericiguat or matching placebo followed by 2 dose doublings in 2-week intervals to reach the 10 mg dose, dependent on the subject's tolerance determined by SBP and symptoms. The primary endpoint was the time to the first occurrence of the composite of CV death or HF hospitalization. Important secondary endpoints included the individual components of the primary endpoint and all-cause mortality.

The randomized parallel-group, placebo-controlled, double-blind, multicentre 12-week dose-finding study (SOCRATES-REDUCED) provided additional efficacy and safety data. In this study, 4 vericiguat dose regiments (1.25 mg, 2.5 mg, 2.5 up-titrated to 5 mg, and 2.5 up-titrated to 10 mg) relative to placebo were evaluated in patients with worsening HFrEF.

3.2. Favourable effects

Primary endpoint. In the pivotal study VICTORIA, treatment with vericiguat resulted in a significant 10% relative hazard reduction in the composite of the first occurrence of either CV death or HF hospitalization (HR 0.90 [95% CI: 0.82, 0.98]; p=0.019). The annualized absolute risk reduction was 4.2%. The benefit of vericiguat treatment was seen early and was sustained for the entire study duration for the primary endpoint.

Vericiguat consistently reduced CV death or HF hospitalization across the investigated subgroups of gender, race, geographic region, HF decompensation index event type, NYHA Class, and use of sacubitril/valsartan.

The beneficial effect of vericiguat was supported by SOCRATES-REDUCED. Although not powered to detect differences in clinical outcomes, exploratory analyses showed a reduced risk in the composite endpoint of CV death and HF hospitalization in the 2.5 to 5 mg and 2.5 to 10 mg dose groups (HR 0.63 [95% CI: 0.30, 1.34] and HR 0.53 [95% CI: 0.25, 1.16], respectively) compared with the placebo group. Similar results were found for the secondary endpoints all-cause death, CV death, CV hospitalization, and HF hospitalization.

Secondary endpoint. The components of the primary endpoint were tested alongside the primary endpoint, without multiplicity correction, and therefore these secondary endpoints are considered exploratory. The analyses showed that the significant beneficial effect in primary composite endpoint is mainly driven by a reduction in HF hospitalization events (n=691 (27.4%) and n=747 (29.6%) in the vericiguat and placebo group, respectively, HR 0.90 [95% CI: 0.81, 1.00]; p=0.048 (exploratory)). The relative risk reduction in CV death was 7% (n= 414 (16.4%) and 441 (17.5%), HR 0.93 [95% CI: 0.81, 1.06]; p=0.269 (exploratory). Consistent with the primary endpoint, treatment with vericiguat reduced the risk of total HF hospitalisation by 9% HR 0.91 [95% CI, 0.84, 0.99]; p=0.023) and 10% in the composite of all-cause mortality or HF hospitalisation (HR 0.90 [95% CI, 0.83 0.98]; p=0.021) compared with placebo. Similarly, as the secondary endpoint CV death, a non-significant positive trend in reduced risk in all-cause mortality was observed (HR 0.95 [95% CI: 0.84, 1.07]; p=0.377).

3.3. Uncertainties and limitations about favourable effects

Subgroups. Heterogeneity of effect with respect to NT-proBNP, EF, eGFR, and age was observed. More specifically, subjects with NT-proBNP values in quartile 4 (> 5314 pg/ml) (HR 1.16 [95% CI: 0.99, 1.35]), ejection fraction ≥ 40 -< 45% (HR 1.05 [95% CI: 0.81, 1.36]), eGFR at baseline ≤ 30 ml/min/1.73 m2 (HR 1.06 [95% CI: 0.83, 1.34]), and ≥ 75 years of age (HR 1.04 [95% CI: 0.88, 1.21]) showed no beneficial effect in the primary endpoint; all had a HR above 1.

Health-related quality of life measures. No clinically relevant differences in KCCQ clinical summary score were reported between the vericiguat and placebo group.

3.4. Unfavourable effects

Adverse events. The system organ classes mostly affected and with a higher rate of reported adverse events in the vericiguat group were "gastrointestinal disorders" (25.3% versus 21.7% in placebo), "vascular disorders" (22.0% versus 20.3%), "nervous system disorders" (18.5% versus 17.55), and "blood and lymphatic system disorders" (10.6% versus 8.4%). The most frequently reported AEs with a higher incidence in the vericiguat group compared with the placebo group were ***anaemia*** (7.6% versus 5.7%), ***dyspepsia*** (2.7% versus 1.1%), ***nausea*** (3.8% versus 2.7%), and ***headache*** (3.4% versus 2.4%). The most frequently reported drug-related AEs with a higher incidence in vericiguat compared with placebo (≥ 0.3% difference) were ***hypotension*** (6.8% [n=172] and 5.9% [n=149], ***dizziness*** (1.5% [n=27] and 0.9% [n=23], ***nausea*** (0.8% [n=19] and 0.2% [n=5], ***orthostatic hypotension*** (0.6% [n=14] and 0.3% [n=8], ***dyspepsia*** (0.6% [n=14] and 0.3% [n=8]), ***gastroesophageal reflux disease*** (0.4% [n=9] and 0% [n=0]).

Adverse events of special interest. ***Hypotension*** was more frequently reported in the vericiguat group than the placebo group (15.4 % and 14.1%, respectively). Comparable results were observed for orthostatic hypotension (1.3% versus 1.0%) and symptomatic hypotension (9.1% versus 7.9%). The percentage of subjects with serious adverse events was 1.3% in the vericiguat group and 1.7% in placebo group for hypotension, 0.2% (n=6) and 0% (n=1) for orthostatic hypotension, and 1.2% and 1.5% for symptomatic. Serious drug-related adverse events were low (0.4% of the subjects in each group for hypotension and only one event of orthostatic hypotension in the placebo group). The differences in hypotension event rate between vericiguat and placebo occurred early persisted throughout the study, indicating that the risk of (symptomatic or orthostatic) hypotension can be adequately managed by careful clinical monitoring.

With respect to ***syncope***, slightly higher incidences in AE and SAE were reported in the vericiguat group compared with placebo (4.0% versus 3.5% and 1.7% versus 1.3%, respectively). However, the percentages in drug-related syncope AE and SAE were similar between the vericiguat and placebo group (0.3% versus 0.4% and 0.1% in each group, respectively), which is reassuring.

There is a slightly higher incidence of ***anaemia*** reported with vericiguat compared with placebo (7.6% versus 5.7%, respectively). Similarly, the percentage of subjects with serious adverse events of anaemia was low, but also slightly higher in the vericiguat group compared with the placebo group (1.6% versus 0.9%). The effect on anaemia is reflected in the proportion of subjects with a decrease in hematocrit of 10 percentage points with a value that was below the lower limit of normal which was higher in the vericiguat group (3.9%) compared with the placebo group (2.2%). Similar findings were noted for subjects with a decrease in haemoglobin ≥3 g/dL with a value below the lower limit of normal (5.0% in the vericiguat group compared with 3.2% in the placebo group). Although none of the (serious) events of anaemia in the vericiguat group was considered treatment-related, anaemia is reported as an adverse reaction in section 4.8 of the SmPC which is in line with the SmPC of riociguat.

There is a higher incidence of ***gastrointestinal (GI)-related AEs*** reported in the vericiguat group (25.3%) compared with the placebo group (21.7%). The percentage of subjects with drug-related adverse events of these specific AEs were 0.3% versus 0.2 % for diarrhoea, 0.8% versus 0.2% for nausea, 0.6% versus 0.3% for dyspepsia, 0.1% versus 0.2% for vomiting, and 0.4% versus 0% for gastroesophageal reflux disease. None of these types of GI events were SAE considered drug-related by the investigator, which reassuring. In addition, GI disorders are also described with other vasodilators, e.g. riociguat, PDE5 inhibitors.

The incidences of ***renal and urinary disorders*** were comparable between the vericiguat group and the placebo group with 17.4% in each group, with a similar percentage of acute kidney injury between both treatment groups (5.3% versus 5.0%). Further, the percentage of AEs and SAE related to study drug was comparable between the vericiguat group and the placebo group (0.3% versus 0.2% and 0.2% each, respectively).

There are no signals of ***hepatoxicity*** or ***QTc*** issues in the data that are provided.

Bone disorders. Undesirable effects were observed on growing bone in non-clinical studies with vericiguat. A mechanistic study with another agent of the same pharmacological class (sGC stimulators), riociguat, performed with healthy male volunteers, did not indicate a risk for effects on bone metabolism. Furthermore, post-marketing safety data with riociguat gave no evidence for an increased risk of adverse events on the bone. Moreover, although limited, safety data of the main part of a 6 months open-label uncontrolled study with riociguat in children aged 6 to <18 years with PAH (PATENT-CHILD), did not show bone and/or growth anomalies in this population. Statements regarding bone effects in nonclinical studies with vericiguat was included in sections 4.2 and 5.3 of the SmPC.

Serious adverse events. The incidence of SAE was relatively high; however, a slightly lower in the vericiguat group compared with the placebo group (32.8% versus 34.8%). The incidence in drug-related SAEs was slightly higher in the vericiguat group compared with the placebo group (1.2% versus 0.8%); however, no pattern indicative for a safety signal could be identified among the types of drug-related SAEs, which is reassuring.

Deaths. All-cause mortality was lower for vericiguat compared with placebo, in line with the efficacy data.

Tolerability. The 10 mg dose of vericiguat was well tolerated since the majority of the subjects who reached the 10 mg dose (vericiguat or matching placebo) by week 8 stayed on the target dose for at least 80% of the treatment period, which was also similar in both groups (61.6% and 63.8% for vericiguat and placebo, respectively). The incidence of AEs leading to discontinuations was slightly higher in the vericiguat group compared with the placebo group (6.6% versus 6.3%). The most frequently reported AEs leading to discontinuations with a higher incidence in the vericiguat group compared with the placebo group were ***hypotension*** (1.9% versus 1.3%), ***dyspepsia*** (0.2% versus 0.1%), and ***nausea*** (0.2% and 0.0%), which is in line with the mechanism of action. Nevertheless, the incidences in these AEs leading to discontinuations were low, which is reassuring. Furthermore, no other pattern with respect to the type of AE leading to discontinuation of study drug could be observed.

Subgroups. Adverse event summary evaluations showed that more safety issues occur in patients with advancing **age.** However, no specific pattern indicative for a safety signal across the subgroups could be observed. Furthermore, concerning **patients with hepatic impairment**, in VICTORIA, subjects with mild and moderate hepatic impairment were allowed to be enrolled, and no differences in safety profiles between the ALBI score grades 1 and 2 have been identified. Furthermore, patients above 75 years of age, patients with moderate renal impairment, patients not using MRAs at baseline, and patients with systolic BP at baseline of < median were not more vulnerable to the hypotensive

effect of vericiguat. With respect to **patients with renal impairment**, the difference between the vericiguat and the placebo group with respect to drug-related adverse events, serious drug-related adverse events, and discontinuation of study drug due to an adverse event is greater in the ≤ 30 mL/min/1.73m^2 subgroup compared with the >30 - ≤ 60 mL/min/1.73m^2 and the > 60 mL/min/1.73m^2 subgroups. However, no specific pattern in the type of (serious) drug-related adverse events or type of AE leading to discontinuation indicative for a safety signal could be observed, which the exception of renal and urinary disorders. The Applicant's evaluation of each drug-related event of acute kidney injury or chronic kidney disease, supplemented with the patient narratives showed that concomitant diseases, medications or other events constitute more plausible alternative explanations for the observed differences in events. As such it is concluded that patients with severe (eGFR ≤ 30 mL / min / 1.73 m2) or moderate (eGFR > 30 to ≤ 60 mL/min/1.73 m2) renal impairment are not more vulnerable to renal and urinary disorders, i.e. acute kidney injury or chronic kidney disease, upon treatment with vericiguat.

3.5. Uncertainties and limitations about unfavourable effects

A slightly higher percentage of patients treated with vericiguat compared with placebo experienced an adverse event of hypotension at the 2.5 mg and 5 mg dose, whereas the percentage of patients with hypotension was generally comparable between vericiguat and placebo at the 10 mg target dose.

Although there were consistent results with respect to slightly higher incidences in symptomatic hypotension observed in the subgroup analyses with respect to NYHA class and use of sacubitril/valsartan, the subgroup analyses of CCSA showed inconsistent results, probably due to the limited number of subjects with angina.

3.6. Effects Table

Table 48. Effects Table for vericiguat in patients with HFrEF (VICTORIA)

Effect	Short Description	Unit	Vericiguat	Placebo	Uncertainties/ Strength of evidence
Favourable Effects					
Primary endpoint	**Composite endpoint of CV death or HF hospitalization**	N (%)	897 (35.5)	972 (38.5)	**SoE**: HR 0.90 [95% CI: 0.82, 0.98]; p=0.019 **Unc:** detrimental/neutral effect in subgroups characterized by increased levels of NT-proBNP, higher EF, lower eGFR, and increased age
Secondary endpoint	**CV death**	N (%)	414 (16.4)	441 (17.5)	**SoE:** HR 0.93 [95% CI: 0.81, 1.06]; p=0.269 (exploratory)
	First HF hospitalization	N (%)	691 (27.4)	747 (29.6)	**SoE:** HR 0.90 [95% CI: 0.81, 1.00]; p=0.048 (exploratory)
	Total HF hospitalization	N (follow-up time in years)	1223 (3190.7)	1336 (3151.0)	**SoE:** HR 0.91 [95% CI: 0.84, 0.99]; p=0.023
	Composite of all-cause mortality or HF hospitalization	N (%)	957 (37.9)	1032 (40.9)	**SoE:** HR 0.90 [95% CI: 0.83, 0.98]; p=0.021

Effect	Short Description	Unit	Vericiguat	Placebo	Uncertainties/ Strength of evidence
	All-cause mortality	N (%)	512 (20.3)	534 (21.2)	**SoE**: HR 0.95 [95% CI: 0.84, 1.07]; p=0.377
Unfavourable Effects					
Hypotension		%	15.4	14.1	**SoE:** Difference in hypotension event rates occurred early and persisted throughout the study
	Symptomatic hypotension	%	9.1	7.9	
	Orthostatic hypotension	%	1.3	1.0	
	Syncope	%	4.0	3.5	
Anaemia		%	7.6	5.7	**SoE:** Anaemia events have been previously reported with another sGC stimulator, riociguat.
GI disorders		%	25.3	21.7	**SoE:** A GI effect has been previously reported with another sGC stimulator, riociguat. GI events included diarrhoea, nausea, dyspepsia, vomiting, gastroesophageal reflux disease

Abbreviations:
CV: Cardiovascular
HF: Heart failure
SoE: Summary of effect
Unc: Uncertainty

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The current application is based on a single pivotal study VICTORIA, which was a well-conducted study. The investigated endpoints are robust outcomes and relevant to HFrEF patients.

Results show a significant but modest improvement in the composite endpoint of CV death and HF hospitalisation in patients administered vericiguat compared with placebo. This effect was mainly driven by a reduction in HF hospitalization events. The beneficial effect on the primary endpoint (HR 0.90 [95% CI: 0.82, 0.98], p=0.019) seems smaller than anticipated and smaller than those found in other HF trials (HR 0.80 [95% CI: 0.73, 0.87]; p<0.001 for sacubitril/valsartan compared with enalapril in PARADIGM-HF and HR 0.74 [95% CI: 0.65, 0.85]; p<0.001 for dapaglifozin compared with placebo in DAPA-HF). Nevertheless, the effect of vericiguat is regarded as being clinically relevant considering that patients who had symptomatic heart failure with reduced ejection fraction and who had recently been hospitalized or had received intravenous diuretic therapy such as those studied in VICTORIA were patients at high risk despite guideline-based medical therapy, which included angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB) (73%), beta-blockers (93.1%), mineralocorticoid receptor antagonists (MRA) (70.3%), and a combination of an angiotensin receptor and neprilysin inhibitor (ARNI) (15%). 91% of patients were treated with two or more heart failure medications (beta-blocker, any renin-angiotensin system [RAS] inhibitor, or MRA),

and 60% of patients were treated with all 3. Additionally, 2.7% of subjects were receiving sodium-glucose co-transporter-2 (SGLT2) inhibitors. This very high risk is confirmed by the high number of events in this population (37.8 primary endpoint events per 100 patient-years at risk in the placebo group), which was 2 to 3 times higher than those observed in other recent HFrEF trials. The absolute risk reduction (ARR) and number needed to treat (NNT) take into account these event rates and, thus, reflect risk level as compared to the HR. The ARR of 4.2 events per 100 patient years found in the VICOTRIA trial converts into a number needed to treat (NNT) of 24 patients per year to prevent one primary composite outcome event. This NNT is comparable with the NNT observed in other recent HF studies, among which the DAPA-HF trial (NNT of 25), which was the basis for the extension of the indication "treatment of HF" for dapagliflozin.

Further, although the VICTORIA trial is adequately conducted with a low amount of missing data and strict adherence to GCP, the proof of efficacy still relies on the results from one pivotal trial. Nevertheless, the results of the phase 2 study SOCRATES-REDUCED supplement the strength of statistical significance from the primary endpoint of VICTORIA, since this study, although not powered to detect differences in clinical outcome, also showed lower event rates in the composite endpoint of CV death and HF hospitalization (in the 2.5-10 mg vericiguat compared with the placebo group (n=10 (11.0%) and n=18 (19.6%), HR 0.53 [95% CI: 0.3, 1.16] (exploratory).

The lack of effect observed in the subgroups of NT-proBNP (> 5314 pg/ml), eGFR (< 30 ml/min/1.73m^2 and age (>75 years) observed in VICTORIA, suggested that vericiguat might not be appropriate in these more vulnerable, compromised group of patients. Post-hoc multivariate analysis (Patient Response Identifiers for Stratified Medicine [PRISM]) only identified NT-proBNP as the most influential predictor of different treatment responses, whereas age and eGFR were not. It is acknowledged that NT-proBNP is a dynamic marker, which is usually significantly increased at a decompensation event. This is confirmed by the observation that the NT-proBNP value was highest in patients enrolled earlier after the index HF hospitalization in the VICTORIA trial (mean NT-proBNP of 7275 pg/mL during index event of HF hospitalization and 4764 pg/ml, 4867 pg/ml and 5209 pg/ml discharged within 10 days, between 10-30 days or between 30-60 days, respectively), whereas patients enrolled later (i.e. > 60 days after discharge) these values were lower (NT-proBNP of 4309 pg/ml). Additionally, the HR for the composite primary endpoint of CV death and HF hospitalization was numerically lower in patients enrolled following a period of 1-2 months after HF hospitalization (HR 0.79) when compared to patients enrolled within 1 month after HF hospitalization (HR 1.01), which questions whether patients who were enrolled within 1 month after HF hospitalization were clinically stable and could benefit from treatment with vericiguat. These findings suggest that patients with very high NT-proBNP reflect clinically unstable patients who require further optimizing of SoC. In this respect, the recommendation was included in section 4.2 to initiate of vericiguat therapy only after optimised SoC, particularly in patients with very high NT-proBNP levels, to reflect the target population appropriate for vericiguat therapy.

The subgroup of EF >40%-45% showed no beneficial effect. According to the ESC guidelines for the diagnosis and treatment of acute and chronic heart failure (2016), patients with EF < 40% (HF with reduced EF (HFrEF)) and patients with EF 40-49% (HF with mid-range EF (HFmrEF) represent two different populations due to underlying aetiologies, demographics, co-morbidities and most importantly response to therapies. Moreover, no treatment has been shown to reduce morbidity or mortality in patients with EF> 40% (CHARM-Preserved (candesartan), I-PRESERVE (irbesartan), TOPCAT (spironolactone)). In addition, in SOCRATES-PRESERVED, treatment with vericiguat in patients with EF> 45% did not demonstrate changes in NT-proBNP. Based on the above, it is considered appropriate to use a more general indication "*with reduced ejection fraction*" with a cross-reference to section 5.1 for information on EF in line with other recently approved medicinal products for the treatment of the chronic heart failure (e.g. sacubitril/valsartan).

Safety data are primarily based on the pivotal phase 3 study VICTORIA, providing a mean exposure of 362.0 days for 2063 subjects treated with 10mg vericiguat. The documented safety exposure exceeds the requirements of ICH-E1 and is considered sufficient for adequate assessment of the safety profile of vericiguat. The most frequently reported AEs are mainly related to the mechanism of action of vasodilation, including hypotension, headache and nausea or in line with another sGC stimulator (riociguat), including anaemia and GI disorders. Vericiguat is well-tolerated since the majority of the AEs are mild to moderate in severity, and the discontinuations due to adverse events are low. Concerning to the AEs of special interest, hypotension events occurred early and can be adequately managed by careful clinical monitoring.

3.7.2. Balance of benefits and risks

The documented benefits of vericiguat in terms of a significant reduction in the composite endpoint of CV deaths or HF hospitalization are considered to be of clinical relevance and to outweigh the risk. Further, very likely not all patients enrolled in VICTORIA were clinically stable, due to the design of VICTORIA which allowed earliest possible randomization after initial hemodynamic stabilization, which may have resulted in the lack of beneficial effect in the more vulnerable, comprised groups of patients, i.e. patients with baseline NT-proBNP $\geq$ 5314 pg/mL, age $\geq$ 75 years, and eGFR $\leq$ 30 mL/min/1.73 m^2. Consequently, vericiguat therapy should only be initiated after optimising volume status and diuretic as well as other HF therapies, particularly in patients with very high NT-proBNP levels.

3.8. Conclusions

The overall B/R of Verquvo is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Verquvo is favourable in the following 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 (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that vericiguat is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

No significant studies in the agreed paediatric investigation plan P/0070/2017 have been completed, in accordance with Article 45(3) of Regulation (EC) No 1901/2006, after the entry into force of that Regulation.