CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214377Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	NDA 214377 Vericiguat
Priority or standard	Priority
Submit date(s)	5/21/2020
Received date(s)	5/21/2020
PDUFA goal date	1/20/2021
Division/office	Division of Cardiology and Nephrology (DCN)
Review completion date	1/19/2021
Established name	Vericiguat
(Proposed) trade name	VERQUVO
Pharmacologic class	SGC stimulator
Code name	MK-1242
Applicant	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc
Dose form/formulation(s)	2.5 mg, 5 mg and 10 mg oral tablet
Dosing regimen	Start 2.5 mg once daily (taken with food) and double the dose every 2 weeks to reach the target maintenance dose of 10 mg once daily
Applicant proposed indication(s)/population(s)	To reduce the risk of cardiovascular death and hear failure (HF) hospitalization following a worsening HF event, in adults with symptomatic chronic HF and ejection fraction less than 45%, in combination with other HF therapies.
Proposed SNOMED indication	Heart failure with reduced ejection fraction
Regulatory action	Approval
Approved indication(s)/population(s) (if applicable)	To reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for HF or need for outpatient IV diuretics in adults with symptomatic chronic HF and ejection fraction less than 45%
Approved SNOMED indication	Heart failure with reduced ejection fraction

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Glossary

ACCF	The American College of Cardiology Foundation
ACE	angiotensin converting enzyme
ACEi	angiotensin converting enzyme inhibitor
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AHA	The American Heart Association
ALT	alanine aminotransferase
ARB	angiotensin II receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor
AST	aspartate aminotransferase
BP	blood pressure
BPCA	Best Pharmaceuticals for Children Act
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
cGMP	Cyclic guanosine monophosphate
CI	confidence interval
CiPA	the comprehensive in vitro proarrhythmia assay
CRF	case report form
CRT	cardiac resynchronization therapy with biventricular pacing
CRT-D	CRT device with defibrillation capability
CSR	clinical study report
CV	cardiovascular
DBP	diastolic blood pressure
DPMH	Division of Pediatrics and Maternal Health
DSMB	Data & Safety Monitoring Board
EC	Executive Committee
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
EFD	embryo-fetal development
EOP2	end-of-phase 2
EQ-5D	EuroQol- 5 Dimension
FDA	Food and Drug Administration
FMQ	FDA MedDRA queries
GCP	good clinical practice
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
HRQoL	health related quality of life
IC_{50}	half maximal inhibitory concentration

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ICD	implantable cardioverter-defibrillator
ICH	International Conference on Harmonization
IND	investigational new drug
ISS	integrated summary of safety
ITT	intention-to-treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
MRA	mineralocorticoid receptor antagonist
NO	nitric oxide
LLN	lower limit of normal
LOCF	last observation carried forward
LVEDP	left ventricular end diastolic pressure
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRA	mineralocorticoid receptor antagonist
MRHD	maximum recommended human dose
NDA	new drug application
NNT	number needed to treat
NOAEL	no observed adverse effect level
NYHA	New York Heart Association
OCP	Office of Clinical Pharmacology
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PDE5	phosphodiesterase type 5
PeRC	Pediatric Review Committee
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PT	preferred term
QTc	corrected QT interval
RAS	renin-angiotensin system
REMS	risk evaluation and mitigation strategy
RTS	Pharm-Tox Coordinating Committee Reproductive Toxicology Subcommittee
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
Sitting SBP	sitting systolic blood pressure
SCD	sudden cardiac death
SOC	system organ class
SD	standard deviation
sGC	soluble guanylate cyclase

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SGLT2-i	sodium-glucose transport protein 2 inhibitor
SMQ	standardized MedDRA queries
TEAE	treatment-emergent adverse event
TQT	thorough QT
ULN	upper limit of normal
VICTORIA	**V**er**IC**igua**T** Gl**O**bal Study in Subjects With Heart Failure With **R**educed Eject**I**on Fr**A**ction

I. Executive Summary

1. Summary of Regulatory Action (CDTL)

Vericiguat is a soluble guanylate cyclase (sGC) stimulator developed for the treatment of chronic heart failure (HF). Soluble guanylate cyclase stimulates production of cGMP, a signaling molecule involved in vascular smooth muscle relaxation, cardiac contractility, and cardiac remodeling. It is proposed that vericiguat can help remediate deficiencies in intracellular cGMP levels, thus improving myocardial and vascular function via vasodilation and reduction of cardiac afterload.

The review team recommends approval of vericiguat (VERQUVO) to reduce the risk of cardiovascular (CV) death and HF hospitalization following a hospitalization for HF or need for outpatient IV diuretics in adults with symptomatic chronic HF and an ejection fraction less than 45%.

Evidence for efficacy is based on VICTORIA, a randomized, double-blind, event-driven, international trial (N=5050) comparing vericiguat (up to the target maintenance dose of 10 mg once daily) and placebo in adult patients with chronic HF with reduced ejection fraction (HFrEF) defined by a left ventricular ejection fraction (LVEF) less than 45%, NYHA Class II-IV symptoms, and an elevated natriuretic peptide level following a worsening HF event. Most enrolled patients were receiving HFrEF medications that were standard-of-care therapies at the time of enrollment (background sacubitril/valsartan use was low, and SGLT2 inhibitors [SGLT2-i] were not yet approved for this indication during the enrollment period). VICTORIA demonstrated a statistically significant effect on its primary endpoint, the time to first occurrence of CV death or HF hospitalization (HR: 0.90, 95% CI: 0.82, 0.98; p = 0.019). A trend toward benefit with respect to the composite outcome was present in most subgroups, with the exception of subjects in the highest quartile of NT-proBNP at baseline (see review issue below). Vericiguat treatment resulted in a 10% relative hazard reduction and an annualized absolute risk reduction of 4.2% compared to placebo. Therefore, on average, 24 patients would need to be treated for 1 year to prevent 1 primary endpoint event. Both CV death and HF hospitalization favored vericiguat and contributed to the overall treatment effect.

The major clinical review issue for this NDA was related to information suggesting that CV death and sudden cardiac death (SCD) occurred more frequently in some vericiguat-treated

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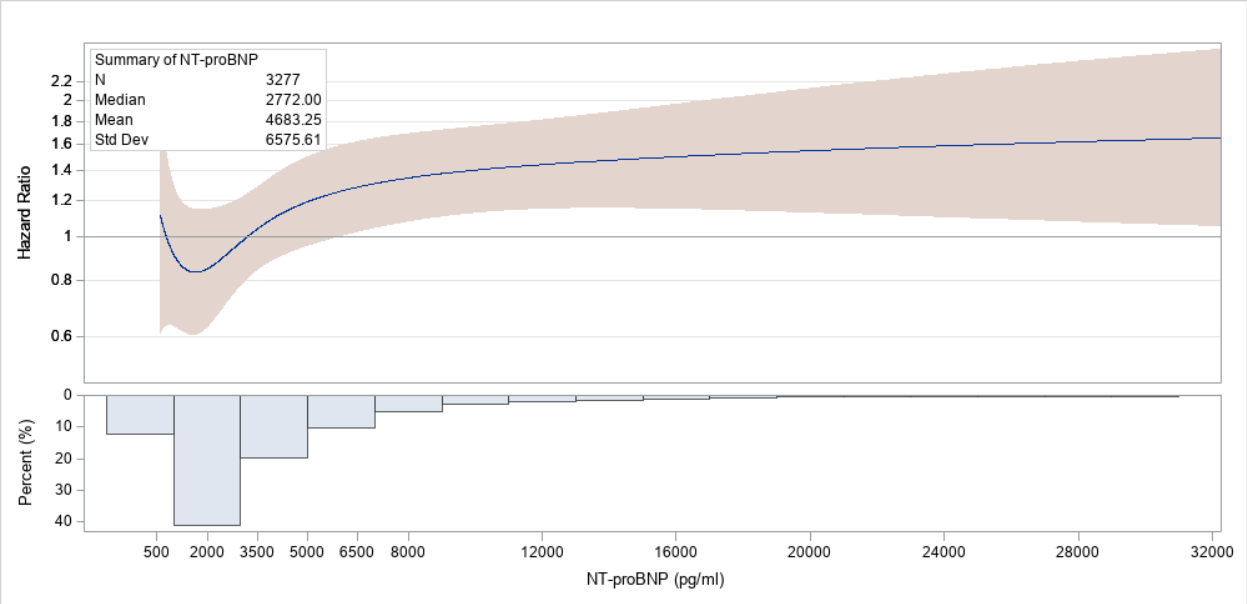
subjects. Specifically, the results of VITALITY, a trial of vericiguat in subjects with HF with preserved ejection fraction (HFpEF, LVEF ≥ 45%), became available just before the submission of this NDA. In that 6-month placebo-controlled trial of 789 patients with HFpEF and LVEF ≥ 45%, CV death occurred in 3.8% of vericiguat treated patients compared to 1.5% of placebo treated patients, including sudden cardiac death (SCD) in 2% of vericiguat-treated patients compared to none of the placebo-treated patients. (b) (4)

It was in this context that we observed and were concerned that in VICTORIA, a higher incidence of CV death occurred in vericiguat-treated patients compared to the placebo-treated patients in the subset of those in the highest baseline NT-proBNP quartile (> 5300 pg/mL, N = 1201, 208 deaths [34%] vs.169 deaths [29%], respectively). In this subset, SCD occurred in 9.1% of vericiguat-treated patients compared to 6.7% of the placebo-treated patients.

Of note, the subgroup analysis of the primary efficacy outcome by NT-proBNP quartile was pre-specified in the VICTORIA statistical analysis plan. In a *post hoc* analysis, it was further concerning that a strong/significant interaction was seen for the outcome of CV death by the presence versus the absence of an implantable cardioverter-defibrillator (ICD) at baseline (HR: 0.69, 95% CI: 0.55, 0.88 versus HR: 1.06 95% CI: 0.90,1.25, respectively, interaction p = 0.004).

From VICTORIA, a multivariate analysis of the hazard ratio for CV death as a continuous function of NT-pro-BNP, by baseline device-use, among subjects in the ITT population with an available NT-proBNP and device-use status at baseline (N = 4804) was performed as displayed in the following two figures:

Hazard Ratio for CV mortality by NT-proBNP among Subjects Without Device (~68% of ITT Population)



* ITT population with available baseline NT-proBNP level and device use (N =4804). See section 5.4.2 and Figure 9 for details about the analysis

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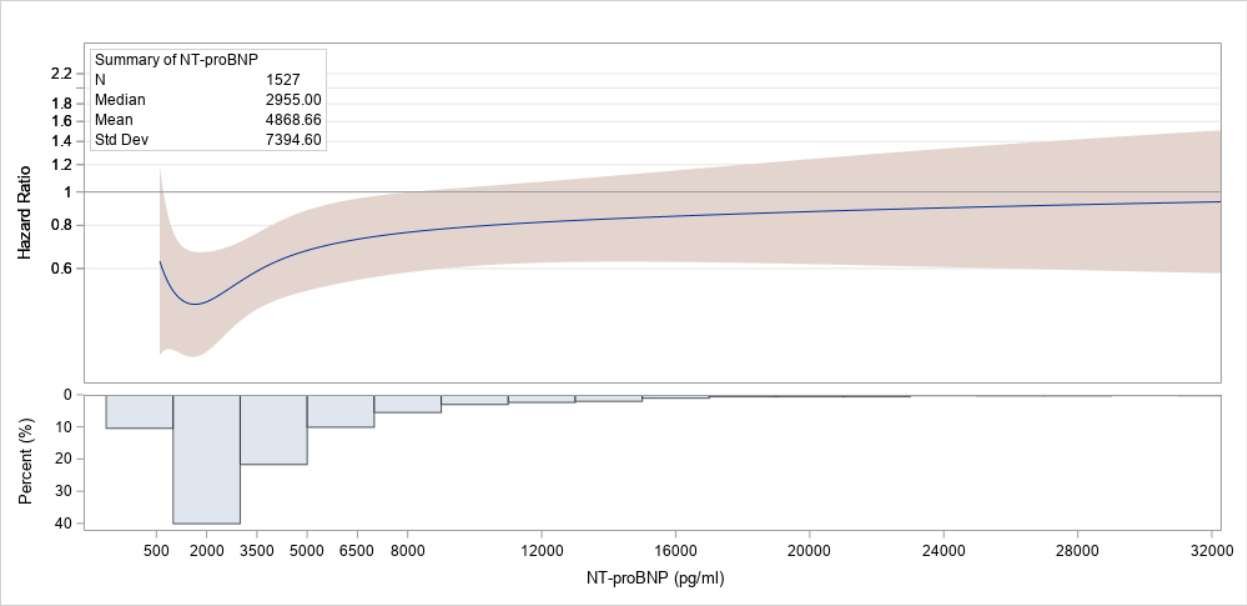
Hazard Ratio for CV mortality by NT-proBNP among Subjects with Device (~32% of ITT Population)



* ITT population with available baseline NT-proBNP level and device use (N =4804). See section 5.4.2 and Figure 9 for details about the analysis

The difference in CV death between patients with vs. without a device suggests that vericiguat is pro-arrhythmic, and that these devices are protective. Downloads of ICD intracardiac electrograms from these VICTORIA subjects were not collected during the trial. Therefore, it was not possible to ascertain whether devices were or were not delivering appropriate therapies (shocks or anti-tachycardia pacing) with an increased frequency compared to baseline in subjects treated with vericiguat.

Because of these observations, a focused search for a potential mechanism for vericiguat-induced proarrhythmia ensued and provided the following reassuring information that vericiguat is not proarrhythmic:

- An absence of reported adverse events (AEs) related to vericiguat-induced life-threatening ventricular arrhythmias
- A thorough QT (TQT) study that excluded large vericiguat changes in the QTc interval (design limitations precluded the ability to ascertain small vericiguat-induced changes in the QTc interval)
- Detailed cardiac channel voltage clamping studies (including CiPA-compliant repeat studies) of hERG, IKs, CaV1.2, and NaV1.5 were performed during the NDA review period, including frequency and holding voltage effects on the relevant potassium and sodium currents to simulate the “worst case clinical scenarios” of beta-blocker-associated bradycardia as well as ischemia-related increases in baseline holding potentials. All of the IC-50 values of these studies were remarkably high, showing no

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potential mechanism for membrane-channel interactions that would produce an arrhythmogenic substrate.

- From VITALITY, the numbers of subjects with SCD were small, and there was no dose-response: 1.9% (5/263) of patients treated with vericiguat 10 mg, 1.9% (5/264) of patients treated with vericiguat 15 mg, and 0% (0/262) of patients treated with placebo.

At the late cycle meeting with the applicant, it was agreed that it would be appropriate to disclose the prespecified VICTORIA trial efficacy outcome result (and components) by NT-proBNP quartile, in that this was a prespecified analysis, (b) (4) in labeling, (b) (4)

The major potential risks explored in the clinical safety data include symptomatic hypotension, syncope, and anemia. Symptomatic hypotension and syncope are potentially related to the vasodilatory mechanism of action of vericiguat; however, syncope and symptomatic hypotension adverse events were not associated with serious events such as increased falls or fractures and the majority of subjects remained on treatment with their doses unchanged. Anemia and decreases in hemoglobin did not result from increased clinical bleeding and did not cause untoward clinical consequences. Therefore, it is the opinion of the clinical reviewers that these risks can be managed and adequately addressed through labeling.

An additional risk of embryo-fetal toxicity was identified based on findings in rats and rabbits. This risk may be related to the pharmacologic class, as similar findings have been observed with another soluble guanylate cyclase (sGC) stimulator for which a risk evaluation and mitigation strategy (REMS) is required for dispensing. Several factors were considered regarding the approach to risk mitigation for vericiguat in the post marketing setting (e.g., prevalence of HFrEF in females of child bearing potential, labeling for other drugs used to treat the condition, burden introduced by the REMS on access to medication) and the matter was discussed with the REMS Oversight Committee. The review team, with concurrence of the REMS Oversight Committee, concludes that the embryofetal risk can be addressed via labeling (boxed warning) and postmarketing surveillance for pregnancy exposure.

The following table provides the review conclusions and recommendations from the other disciplines that reviewed this application:

Discipline	Key Review Conclusions
Toxicology	• Bone effects were most apparent in the shorter-term studies using adolescent rats and included hypertrophy of the growth plate, hyperostosis, and remodeling of metaphyseal and diaphyseal bone. These effects were not reported in the definitive juvenile animal study or

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	the 2-year carcinogenicity studies. These findings are described in Section 13 of the proposed label. • Early in development, urinary crystals were reported for both rats and dogs. These were insoluble crystals described as resembling sea urchins. About this, the applicant presented plausible data that this was due to level of urinary vericiguat excretion in the rats which was about 40X greater than humans. There were no findings relative to urinary crystals in the chronic toxicology studies, and the FDA toxicology reviewer agreed that it is not a significant potential signal from the nonclinical perspective. Follow-up assessment of the clinical safety database for this NDA showed no imbalances of urinary tract adverse events. • The cardiovascular safety pharmacology suggested effects on several ion channels. In vitro, the parent drug achieved 50% inhibition of the hERG channel at 10μM. Conscious telemetered Beagles showed a dose-related prolongation of the PR interval by approximately 16% of baseline along with a slight (2%) change in duration of the QRS interval. • The primary nonclinical reviewer interpreted the embryo-fetal development studies (EFD) to indicate fetal toxicity manifested as malformations in the rabbit study and variations in the rat study related to treatment with vericiguat. The applicant challenged this interpretation on the premise that the malformations were within the range of the historical controls. The matter was presented to the Pharmacology Toxicology Coordinating Committee Reproductive Toxicology Subcommittee (RTS) for consultation. • The RTS interpreted the results of the rabbit EFD as demonstrating treatment-related malformations. • The RTS recommended that the treatment-related embryo-fetal effects be described in the label.
Clinical Pharmacology	• The to-be-marketed formulation is the same as the clinical trial formulation. • No dose adjustment is necessary in patients based on gender, body weight, race and ethnicity. • No dose adjustment is necessary in patients with estimated glomerular filtration rate (eGFR) ≥15 mL/min or not on dialysis. Vericiguat has not been studied in patients with eGFR <15 mL/min at treatment initiation or on dialysis. • No dose adjustment is necessary in patients with mild and moderate hepatic impairment. Vericiguat has not been studied in patients with severe hepatic impairment. • No dose adjustment is necessary with other concomitant medications. • Not recommended for use with PDE5 inhibitors because of limited clinical experience in patients with HFrEF.
OPQ/CMC	• From the Chemistry, Manufacturing and Controls (CMC)/quality perspective, NDA 214377 Vericiguat Tablet is recommended for

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	approval. As part of this action, an expiration period of 36 months is granted for the product, when stored at controlled room temperature of 20°C to 25°C (68°F to 77°F) in the purposed commercial packaging, consisting of either HDPE bottles or blister packs.
OSI	• Remote regulatory assessment of Dr. Hans Prozesky and Dr. Clara Saldarriaga were conducted in support of this application. Based on the results of these investigations, the study (Protocol P001MK1242) appears to have been conducted adequately, and the data generated by the clinical investigator sites appear acceptable in support of the respective indication. • The Coronavirus (COVID-19) global pandemic has significantly limited OSI's ability to conduct on-site GCP inspections, and a remote investigation was not possible for Dr. Pawel Miekus due to The European Union General Data Protection Regulation. As a result, and in an effort to protect the health, safety, and welfare of FDA employees and study staff, the planned inspection of Dr. Pawel Miekus was reevaluated. Following discussions between OSI and DCN, a decision was made that an assessment of the application could proceed without GCP inspection of Dr. Pawel Miekus.
DPMH PLLR	• Teratogenicity was observed in embryo-fetal development studies in rabbits in six difference litters in which pups had cardiac defects (formation of the heart and great vessels). Developmental toxicity studies in rats and rabbits with vericiguat administered orally during organogenesis showed maternal toxicity in rats and rabbits at ≥ 10 and ≥ 6 times, respectively, the human exposure at the MRHD, which resulted in late spontaneous abortions and resorptions in rabbits. • Recommended post-marketing requirement: Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to vericiguat during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The study will collect information for a minimum of 10 years. Results will be analyzed and reported descriptively. Data collected retrospectively will be analyzed separately and reported with the interim and final study reports.
OSE	• ARIA analytic tools are not sufficient to assess the clinical risk of embryo-fetal toxicity because data mining methods have not been tested for birth defects and other pregnancy outcomes. Because broad-based signal detection is not currently available, other parameters have not been assessed. • Recommended post-marketing requirement: as described above.

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2. Benefit-Risk Assessment

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Heart Failure (HF) is a chronic, progressive condition affecting 6 million individuals in the United States. About half of HF patients have HF with reduced ejection fraction (HFrEF). Despite available HF therapies, the mortality and hospitalization rates remain high. The 5-year mortality in HFrEF patients aged ≥ 60 years is approximately 66%. The clinical course for HFrEF patients is variable, but many patients experience acute episodes of clinical decompensation with increased symptoms requiring hospitalization and/or IV diuretic treatment. This worsening of chronic HF is associated with a poor long-term prognosis.	Heart Faiure (HF) is a chronic, progressive condition with significant morbidity and mortality. Worsening of chronic HF is the norm during the clinical course of HFrEF patients and is related to poor prognosis.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	Current treatment options for patients with HFrEF include pharmacologic and device therapies. Approved pharmacologic therapies: • renin-angiotensin inhibitors (ACEi, ARBs, and ARNI), beta-blockers, MRAs, hydralazine with isosorbide dinitrate (for African Americans) and dapagliflozin (approved in 2020) are indicated to reduce HF hospitalization and/or mortality (ACCF/AHA Class I recommendations, 2013 and 2016) • ivabradine is indicated to reduce HF hospitalization • digoxin and diuretics are indicated to improve HF symptoms Approved device therapies to treat patients with HFrEF include the implantable cardioverter-defibrillator (ICD), cardiac resynchronization therapy (CRT, also known as biventricular pacing), and a device combination of both ICD and CRT functionalities (CRT-D).	Despite available treatment options, there is a continued unmet need to reduce morbidity and mortality in patients with HFrEF.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	The effectiveness of vericiguat in HFrEF was evaluated in VICTORIA, an adequate and well-controlled trial. VICTORIA was a double-blind, placebo-controlled, event-driven trial in 5,050 patients with HFrEF (LVEF < 45%) and with a recent HF decompensation. Over a median follow-up of 10.8 months, CV death or HF hospitalization occurred in 897 of 2526 patients (33.6 per 100 patient-years) in the vericiguat group and in 972 of 2524 patients (37.8 per 100 patient-years) in the placebo group (HR: 0.90; 95% CI: 0.82-0.98; *p*=0.019). This 10% reduction in the primary composite endpoint translated to an *annualized absolute risk reduction of 4.2% for vericiguat relative to placebo.* Therefore, on average, 24 patients would need to be treated for 1 year to prevent 1 primary endpoint event. *Both CV death (HR: 0.93; 95% CI: 0.81-1.06) and first HF* hospitalization (HR: 0.90; 95% CI: 0.81-1.00) trended to the direction favoring vericiguat.	VICTORIA demonstrated the beneficial effect of vericiguat compared to placebo in reduction of HF hospitalization and CV death in patients with HFrEF following a worsening HF event.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	Vericiguat's treatment effect was generally consistent across subgroups based on demographic and clinical characteristics, with two exceptions: • Unfavorable efficacy results in subjects in the highest baseline NT-proBNP quartile (> 5314 pg/mL) were observed for both CV death (HR: 1.16; 95% CI: 0.95-1.43) and first HF hospitalization (HR: 1.19; 95% CI: 0.9-1.44). In particular, the excess CV death in this subset was driven by a higher incidence of sudden cardiac death in vericiguat-treated subjects. • Differential treatment effects by device use at baseline (i.e., ICD or biventricular pacemaker use) were observed for CV death. Specifically, the protective effect of vericiguat for CV mortality was considerable among subjects with the presence of one of these devices (HR: 0.69 and 0.65 for ICD and biventricular pacemaker presence at baseline, respectively). In contrast, HR was close to or greater than 1 among subjects without a device at baseline. The unfavorable trend in CV death was most notable among those in the highest baseline NT-proBNP quartile without a device at baseline (HR 1.38; 95% CI: 1.08-1.75). Multivariate analyses indicate that the HR for both CV death and HF hospitalization increase as baseline NT-proBNP increases. In *post hoc* exploratory analysis, unfavorable CV mortality (HR > 1) was only observed in subjects without a device at baseline and with baseline NT-proBNP > 3000 pg/mL. In the context of excess sudden cardiac death identified in the trial of vericiguat in heart failure with preserved ejection fraction (HFpEF), VITALITY, these findings raised concern with respect to proarrhythmic effects of vericiguat. However, there were no	The differential results of CV mortality by baseline NT-proBNP and presence/absence of a cardiac device raised concerns with respect to proarrhythmia, particularly in patients with advanced HF and high NT-proBNP who lacked the presence of a defibrillator-capable device at baseline. However, having carefully considered the data from the nonclinical studies, VICTORIA, and a TQT study, we were reassured that there was no corroborative evidence of a proarrhythmic effect of vericiguat (as a negative competing effect along with the benefits of its vasodilatory primary mechanism of action). Nevertheless, given the CV mortality findings observed in the HFpEF program and the unfavorable efficacy/CV mortality trends in the highest baseline NT-proBNP quartile of VICTORIA, these observations will be disclosed in labeling.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	supportive findings indicating proarrhythmic effects of vericiguat from the TQT study or the ECG data in VICTORIA. Excess adverse events (AEs) indicative of life-threatening ventricular arrhythmias were not observed in VICTORIA. Preclinical studies, including CiPA-compliant assays of cardiac channel currents, did not demonstrate a possible mechanism for the *post hoc* clinical finding related to baseline cardiac device use. For vericiguat, symptomatic hypotension and synope were adverse events of special interest (AESIs), and anemia was a potential adverse drug reaction (ADR), arising from the safety profile of another drug in this class (riogicuat). In VICTORIA, the proportions of these events in the two treatment arms were as follows: • Symptomatic hypotension (9.1%) compared with placebo (7.9%) • Syncope (4.0%) compared with placebo (3.5%) • Anemia (9.7%) compared with placebo (7.4%) In animal reproduction studies, malformations of the heart and major vessels, as well as increased numbers of abortions and resorptions, were observed with oral administration of vericiguat to pregnant rabbits during organogenesis, at ≥ 4 times the human exposure with the maximum recommended human dose (MRHD) of 10 mg. In nonclinical toxicology studies, vericiguat-induced adverse effects were observed for doses that exceeded a maximally tolerated dose. The bone effects were most apparent in shorter-	Symptomatic hypotension and syncope are related to the vasodilatory mechanism of action. These events were not associated with serious events, such as increased falls or fractures, and the majority of subjects remained on treatment with doses unchanged. Anemia and decreases in hemoglobin did not result from increased clinical bleeding and did not cause untoward clinical consequences. These risks can be managed and adequately addressed through labeling. Embryo-fetal toxicity was observed in the nonclinical studies. Use in pregnancy can be adequately mitigated via labeling, including a boxed warning, contraindication for pregnancy, and recommendation to obtain a pregnancy test in females of reproductive potential prior to initiating treatment. Post-marketing data on pregnancy exposure will be collected as a PMR. Based on a consult from the former Division of Bone, Reproductive, and Urologic Products (DBRUP) regarding the risks of bone effects in pediatric patients for another sGC stimulator in 2013, the Division is of the opinion that the Pediatric Research Equity Act (PREA) requirement for pediatric studies should be deferred pending the completion of a comprehensive juvenile animal study performed as a post-market requirement

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	term studies of adolescent rats and included hypertrophy of the growth plate, hyperostosis, and remodeling of metaphyseal and diaphyseal bone. Hyperostosis appears to be a class effect of sGC stimulators, though the prominence of this change may be related to molecule-specific bone-penetration. Specific concerns are for drug-induced growth abnormalities caused by hyperostosis of the metaphyseal growth plate of the long bones, and the potential for neurological compression syndromes caused by hyperostosis at the small bony foramina through which axial and cranial nerves traverse.	(PMR) to determine the ages and doses of vericiguat that may be safe and effective for the treatment of dilated cardiomyopathy (DCM) in children. Given that the effects of hyperostosis have been most prominent in young animals during periods of rapid bone growth, as well as the consult from the former DBRUP on this subject, the Division is of the opinion that it would be reasonable to allow pediatric studies to proceed in adolescents concurrently with the required preclinical juvenile animal toxicology study. That juvenile animal toxicology study would then guide the potential enrollment of subsequent younger cohorts of children with DCM. The Division of Cardiology and Nephrology has reconsulted the Division of General Endocrinology (DGE, formerly DBRUP) to assist with the design of both the pre-clinical juvenile animal study and the clinical studies in progressively younger cohorts of children.

Conclusions Regarding Benefit-Risk

The VICTORIA trial demonstrated a statistically significant effect on its primary endpoint, the time to first occurrence of CV death or HF hospitalization (HR: 0.90, 95% CI: 0.82-0.98; p = 0.019). As compared with placebo, this result represents a 10% relative hazard

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reduction of the primary composite endpoint, an annualized absolute risk reduction in primary composite events of 4.2%, and on average, a Number Needed to Treat (NNT) of 24 patients treated for 1 year to prevent 1 primary endpoint event. The annual likelihood of experiencing one of the principal adverse drug reactions (symptomatic hypotension, syncope, and anemia) are in a similar range as the efficacy—approximately 4%. The avoidance of death or hospitalization clearly outweighs these adverse drug reactions, as they were not associated with *harm*, i.e., significant, irreversible, or longstanding morbidity.

A key review issue focused on evaluating an unexpected finding of excess CV death and HF hospitalizations in the quartile of vericiguat-treated subjects with the highest baseline NT-proBNP levels. Preclinical cardiac channel studies, a TQT study, and ECG and AE data from VICTORIA do not demonstrate or suggest a proarrhythmic potential for vericiguat therapy. Nevertheless, the negative trend in CV death and HF hospitalization in this highest baseline NT-proBNP subgroup will be disclosed in labeling. Embryofetal toxicity will be described in labeling (boxed warning for fetal harm and contraindication for pregnancy), and a postmarketing pregnancy surveillance plan will be required. To support dosing in the pediatric population, a preclinical juvenile toxicity study to evaluate bone effects will be required as a PMR, for which PREA studies will be selectively deferred in younger age cohorts of children. In summary, the totality of evidence indicates that the clinical benefit of vericiguat therapy for HFrEF outweighs its potential/theoretical risks, and justifies the approval of vericiguat for the treatment of HFrEF in adults.

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II. Interdisciplinary Assessment

3. Introduction

The applicant has submitted a single, phase 3 trial (VICTORIA) in support of a new drug application (NDA) for vericiguat for the following indication:

> "VERQUVO *is a soluble guanylate cyclase (sGC) stimulator, indicated to reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a worsening HF event, in adults with symptomatic chronic HF and ejection fraction less than 45%, in combination with other HF therapy."*

Disease Background

Heart failure (HF) is a chronic, progressive condition and a major global health concern, affecting 60 million patients worldwide[1]. The annual incidence of HF in the US is > 650,000 cases[2] and it increases with age. About half of these cases are HF with reduced ejection fraction (HFrEF), which is associated with considerable morbidity and mortality. The 5-year mortality in HFrEF patients aged ≥ 60 years is approximately 66%.[3] The clinical course for HFrEF patients is variable, but acute episodes of clinical decompensation requiring hospitalization and/or IV diuretic use are common, and decompensation is associated with a poor long-term prognosis.

Treatment of patients with HFrEF is targeted towards reduction of morbidity/mortality, symptom relief, and the adequate management of comorbidities such as hypertension and atrial fibrillation. ACCF/AHA Class I recommendations for treatments for chronic HFrEF include beta-blockers, renin-angiotensin system (RAS) inhibitors (angiotensin converting enzyme inhibitors [ACEi], angiotensin II receptor blockers [ARB], or angiotensin receptor neprilysin inhibitor [ARNI]), mineralocorticoid receptor antagonists (MRAs), and cardiac device therapies (implantable cardioverter-defibrillator [ICD], cardiac resynchronization therapy with biventricular pacing [CRT], or a CRT device with defibrillation capability [CRT-D]).[2,4-5] Other HF therapies approved to reduce morbidity and/or mortality in patients with HFrEF include hydralazine/isosorbide dinitrate in African Americans, digoxin, ivabradine, and dapagliflozin. Diuretics are used to provide symptomatic relief. Despite the use of these therapies, the rates of CV death and HF hospitalization remain high in patients with HFrEF.

Drug Class

Vericiguat (BAY 1021189/MK-1242) is a new compound that belongs to a class of direct soluble guanylate cyclase (sGC) stimulators. It was co-developed through a joint research and development program between Bayer and Merck Sharpe & Dohme beginning on October 1, 2014. Impairments in the NO-sGC-cGMP signaling pathway are associated with disease progression in HFrEF. VICTORIA was designed to test the clinical hypothesis that by directly

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stimulating sGC and restoring the NO-sGC-cGMP pathway, vericiguat may reduce the occurrence rates of CV death and HF hospitalization.

Clinical Review Issues

- Unfavorable efficacy results in patients with higher baseline NT-proBNP
- Among the cohort of vericiguat-treated subjects with the highest baseline NT-pro-BNP, a strong interaction between the presence of a defibrillator-capable device at baseline with the reduction of CV mortality, suggesting the possibility for competing effects of proarrhythmia (adverse) versus vasodilation (beneficial) in this subgroup
- Embryo-fetal Toxicity

3.1. Approach to the Review

This is a joint clinical and statistical review. Tzu-Yun McDowell and Fanhui Kong focused on the data supporting efficacy. Selena DeConti focused on the data supporting safety. Table 3 below provides a list of clinical trials submitted in support of the efficacy and/or safety determinations for Vericiguat.

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Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Vericiguat

Trial Identifier	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Actual Randomized	Number of Centers and Countries
P002MK1242 SOCRATES-REDUCED (Phase 2)	Patients with HFrEF (NYHA class II to IV, LVEF < 45%) elevated level of natriuretic peptides, and worsening HF at hospitalization (or at the time of IV diuretic treatment for HF without hospitalization)	Randomized, parallel-group, placebo-controlled, double-blind, multicenter, dose-finding study	Drug: Vericiguat/Placebo Dose: 1.25 mg, 2.5 mg, 2.5-5 mg and 2.5-10 mg Number treated: Vericiguat groups 91/90/91/91 Placebo 92 Mean treatment duration was 73.4 days	Primary: Change from baseline to Week 12 in NT-proBNP	456	144 sites (24 countries)

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Trial Identifier	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Actual Randomized	Number of Centers and Countries
P001MK1242 VICTORIA (Phase 3)	Adults (≥18 years), with HFrEF (NYHA class II to IV, LVEF < 45%), elevated level of natriuretic peptides, and previous HF decompensation (HF hospitalization within 6 months or IV diuretic treatment within 3 months)	Randomized, parallel-group, placebo-controlled, double-blind, event-driven, multicenter trial	Drug: Vericiguat/Placebo Dose: 10 mg Number treated: 2519/2515 Mean treatment duration as of the primary completion date (18 Jun 2019) was 362.0 days for vericiguat 10 mg	Primary: Composite of first HF hospitalization and CV death Secondary: 1. CV death 2. First HF hospitalization 3. Total HF hospitalization 4. Composite of all-cause mortality and HF hospitalization 5. All-cause mortality	5050	694 sites (42 countries)
P003MK1242 SOCRATES-PRESERVED (Phase 2)	Patients with HFpEF (NYHA class II to IV, LVEF ≥ 45%) Worsening HF at hospitalization (or at the time of IV diuretic treatment for HF without hospitalization)	Randomized, parallel-group, placebo-controlled, double-blind, multicenter, dose-finding study	Drug: Vericiguat/Placebo Dose: 1.25 mg, 2.5 mg, 2.5-5 mg and 2.5-10 mg Number treated: Vericiguat groups 96/95/95/96 Placebo 94 Mean treatment duration was 73.4 days	Primary: 1. Change from baseline to Week 12 in NT-proBNP 2. Change from baseline to Week 12 in left atrial volume	477	158 sites (25 countries)

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Trial Identifier	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Actual Randomized	Number of Centers and Countries
P032MK1242 VITALITY (Phase 3)	Adults (≥ 45 years), with HFpEF (NYHA class II to III, LVEF ≥ 45%), and previous HF decompensation (HF hospitalization or IV diuretic within 6 month)	Randomized, parallel-group, placebo-controlled, double-blind, multicenter trial	Drug: Vericiguat/Placebo Dose: 10 and 15 mg Number treated: Vericiguat 10/15 mg: 262/264 Placebo: 262 Mean treatment duration was 150 days	Primary: Change in KCCQ PLS from baseline to Week 24	789	178 cites (21 countries)

Source: Reviewer Table
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.

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4. Patient Experience Data

The VICTORIA trial collected data on patients' perceptions of their HF symptoms and health-related quality of life at baseline and at various timepoints using the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the EuroQol- 5 Dimension (EQ-5D). Overall, the results with regard to these measures were similar between the groups (see details in Section 5.3.6.3).

5. Evidence of Benefit (Assessment of Efficacy)

5.1. Assessment of Dose and Potential Effectiveness

The VICTORIA trial evaluated a target dose of 10 mg daily (with dose titration from 2.5 mg to 5 mg to 10 mg based on sitting systolic blood pressure [sitting SBP]). The dose selection and titration regimen for the VICTORIA trial was primarily based on the Phase 2b dose-finding trial (SOCRATES-REDUCED). The SOCRATES-REDUCED trial evaluated four vericiguat dose regimens (1.25 mg, 2.5 mg, 2.5 to 5 mg, and 2.5 to 10 mg) relative to placebo for changes in NT-proBNP from baseline to Week 12 in subjects with HFrEF following a worsening HF event. All treatment groups used 2-week active titration or sham titration intervals to reach their respective dose targets. Titration was based on subject tolerance determined by SBP. The trial did not meet its primary endpoint–there was no difference in the change of NT-proBNP between the pooled three higher dose groups (2.5 mg, 2.5 to 5 mg and 2.5 to 10 mg) and placebo. However, exploratory regression analysis suggested a dose-response trend with the largest decreases in NT-proBNP seen in the 2.5 to 10 mg vericiguat dose group. There were also favorable trends of greater improvement in left ventricular ejection fraction (LVEF) and fewer clinical events in the vericiguat 2.5 to 10 mg group compared to the placebo group; however, the trial was not powered to detect these differences. Hence, a 10-mg target dose was chosen for the VICTORIA trial with a similar titration scheme as was used in SOCRATES-REDUCED.

Reviewer's Comment: At the End of Phase 2 (EOP2) meeting, the Division recommended that a higher dose be studied if possible. Given the uncertainty about the relationship between a modest effect on NT-proBNP and morbidity and mortality, the Division stated that studying a higher dose would be prudent to increase the chance of identifying an efficacious dose.

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5.2. Design of Clinical Trials Intended to Demonstrate Benefit to Patients

5.2.1. Overview of Study

In support of the proposed indication, the applicant conducted a single phase 3 trial titled ”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**igua**T** Gl**O**bal Study in Subjects with Heart Failure With **R**educed Eject**I**on Fr**A**ction (VICTORIA)“. The trial was conducted from September 25, 2016 to September 2, 2019 at 694 sites in 42 countries (8% in the United States).

5.2.2. Initial Protocol and Amendments

The original protocol was finalized on April 1, 2016 and was amended five times (2 general amendments and 3 site-specific amendments [see Appendix III.11.1 for details regarding each amendment]). The overview provided in this section is based on Amendment 1, dated, June 15, 2016, which received final regulatory approval at all sites before the first patient was screened. Further amendments are noted where applicable.

5.2.3. Trial Design

VICTORIA was a randomized, placebo-controlled, parallel-group, multi-center, double-blind, event-driven trial comparing vericiguat to placebo in subjects with HFrEF. The trial design is depicted in Figure 1. The trial enrolled adults ≥ 18 years of age with chronic HF (NYHA Class II-IV) with reduced ejection fraction (< 45%), elevated levels of natriuretic peptides, and previous HF decompensation (defined as HF hospitalization within 6 months before randomization or use of IV diuretics for HF within 3 months before randomization). Eligible subjects were randomized to vericiguat up to 10 mg daily or matching placebo in a 1:1 ratio and stratified according to geographical region and race. Study medication was to be taken in addition to regional standard of care HF therapies.

Study treatment was intended to continue in all randomized subjects until the final study visit. Early discontinuation of study treatment did not represent withdrawal from study follow-up. All subjects were intended to be followed until study completion. The primary completion date of Jun 18, 2019 was prospectively set based on the minimum required number of CV deaths (n = 782), which was projected to have occurred by this date. All primary efficacy and safety endpoints were analyzed by this cutoff date.

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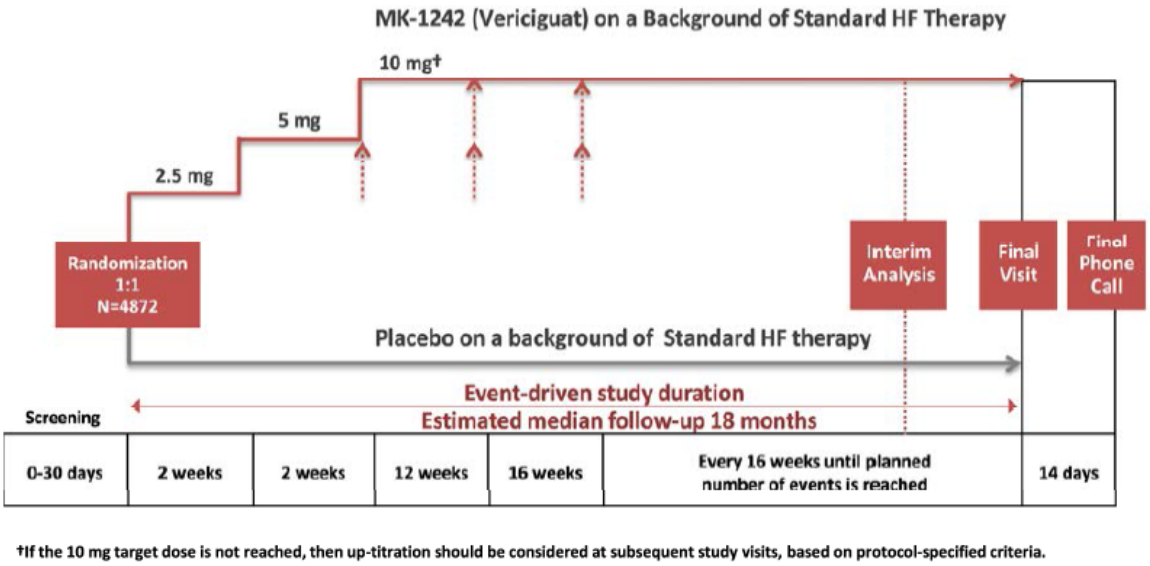
Figure 1 Study Design, VICTORIA



Source: VICTORIA Study Protocol

5.2.4. Study Objectives

The primary objective was to evaluate the efficacy of the oral sGC stimulator vericiguat in comparison to placebo on a background of standard of care in reducing the time to first occurrence of the composite of CV death or HF hospitalization in subjects with HFrEF.

5.2.5. Study Endpoints

Primary efficacy endpoint:

Time to the first occurrence of the composite of CV death or HF hospitalization.

Secondary efficacy endpoints:

- Time to the first occurrence of CV death
- Time to the first occurrence of HF hospitalization
- Time to total HF hospitalizations (first and recurrent)
- Time to the first occurrence of the composite of all-cause mortality or HF hospitalization
- Time to the first occurrence of all-cause mortality

Main Exploratory endpoints:

- Time to the first occurrence of the composite of HF hospitalization or urgent HF visit (not meeting the criteria for a HF hospitalization)
- Time to the first CV hospitalization
- Total number of HF hospitalizations
- Change from baseline to each measurement time point in HRQoL summary measures: KCCQ and EQ-5D

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Potential endpoint events for CV hospitalization, deaths, and urgent HF visits were adjudicated by an independent Clinical Events Committee (CEC). A brief summary of endpoint event identification and triggering processes is described in Appendix III.11.2.

5.2.6. Eligibility Criteria

VICTORIA enrolled chronic HFrEF patients who were being treated with regional standard of care HF therapies and who had experienced a recent worsening HF event.

Key inclusion criteria

- Adults, aged ≥ 18 years
- A history of chronic HF (NYHA class II to IV) on standard therapy before qualifying HF decompensation
- A previous HF decompensation
  - HF hospitalization within 6 months prior to randomization
  - IV diuretic treatment for HF (without hospitalization) within 3 months prior to randomization
- BNP or NT-proBNP levels within 30 days prior to randomization
  - NT-proBNP ≥ 1000 pg/mL or BNP ≥ 300 pg/mL if in sinus rhythm
  - NT-proBNP ≥ 1600 pg/mL or BNP ≥ 500 pg/mL if in atrial fibrillation
- LVEF < 45% within 12 months prior to randomization
- Male or female confirmed to be postmenopausal, without childbearing potential, or use of acceptable contraception

Key exclusion criteria

- Unstable clinical conditions as defined by:
  - Any IV treatment within 24 hours prior to randomization, and/or
  - SBP < 100 mmHg or symptomatic hypotension
- Concurrent or anticipated use of long-acting nitrates or nitric oxide donors
- Concurrent or anticipated use of PDE5 inhibitors
- Concurrent or anticipated used of an sGC stimulator such as riociguat
- Allergy or sensitivity to any sGC stimulator
- Awaiting heart transplantation, receiving continuous IV infusion of an inotrope, or has/anticipates receiving an implanted ventricular assist device.

5.2.7. Data Sources

The applicant's electronic data sources were stored in the subdirectories of \\CDSESUB1\evsprod\NDA214377\0001 of the Center's electronic document. Data sources include all materials reviewed, i.e., study reports, raw data sets in SDTM format, analysis data sets in ADAM format, SAS programs for deriving the data sets and analysis results, protocol amendments, individual data listings, reporting and statistical analysis plan, and literature referenced, etc. The SAS data sets are stored in the directory of

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\\CDSESUB1\evsprod\NDA214377\0001\m5\datasets\. The analysis software is also stored in this same directory.

5.2.8. Data Quality

Per applicant's CSR, the applicant oversaw all clinical activities in accordance with ICH GCP at investigational sites to provide quality assurance and quality control. This included on-site monitoring of source data verification, medical monitoring of clinical study data (including monitoring for protocol deviations), and relevant reviews of regulatory submission documents.

The applicant reviewed all protocol procedures and investigator responsibilities under GCP in meetings prior to study initiation, explaining the conduct of the study and providing instructions to ensure accuracy and consistency in data collection and performance. They also held refresher training sessions with investigation sites throughout the study to review protocol concepts and address trends in protocol non-adherence noted from ongoing trial monitoring.

The applicant assessed data quality through an audit program to ensure adherence with applicable GCP, Good Pharmacovigilance Practices regulations and applicable company policies and procedures. According to the applicant, no subject's data were excluded from the efficacy analyses on the basis of GCP violations.

Reviewer's Comment: The applicant designed and followed specific steps to assure data quality in the VICTORIA trial. The data are well organized that produce the results that matched those of the applicant.

5.2.9. Statistical Analysis Plan

The planned analyses were documented in SAP and supplementary SAP, or contained within protocol amendments. One interim analysis for efficacy was planned in the original SAP at the time when approximately 75% (N=587) of the planned number of CV death events were observed and the median follow up time was at least 10 months. A futility analysis was planned to be performed at the time when approximately 50% (N=781) of the planned number of primary composite events were observed. However, the interim analyses were cancelled by the applicant prior to the unblinded interim analysis due to a higher than expected CV death event rate that would cause the efficacy interim analysis to be too close to the final analysis. Since the timing of the efficacy interim analysis was linked to the futility interim analysis, it too was canceled. The decision to cancel the interim analyses was made by the applicant and Executive Committee (EC) based on the prespecified scenario described in the protocol. The Agency, Data & Safety Monitoring Board (DSMB), and the trial site investigators were informed of the applicant's decision. Statistical analysis procedures and the multiplicity adjustments for the secondary endpoints related to the interim analysis were removed. In addition, the prespecified missingness sensitivity analysis was not conducted because the amount of missing follow-up data was low.

There were no changes in the planned analyses following study unblinding and no *post hoc* analyses were performed for this study report.

Reviewer's Comment: Given that the applicant's decision to cancel the interim analyses was based on the total number of CV death events that occurred before unblinding the interim

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analysis data, this decision did not seem to affect the efficacy results and therefore the type I error rate.

5.2.10. Statistical Analysis Methods

Efficacy analyses were based on the ITT population, which consisted of all randomized subjects that were analyzed according to the planned treatment.

The primary efficacy endpoint was analyzed based on a stratified log-rank test that compared the time to the first event in the composite of CV death or HF hospitalization between the vericiguat and the placebo groups using a 2-sided type I error rate of 0.05. Only clinical events confirmed by the CEC were used in the efficacy analyses. All deaths confirmed by the CEC as having an undetermined cause were included as CV deaths in the analysis. Subjects without an event of HF hospitalization or CV death at the time of the analysis were censored based on the earliest of the following: date of their non-CV death, last available information for the primary endpoint event, or the primary completion date of the study on June 18, 2019.

The secondary endpoints were separated into two families. The first family consisted of the components of the primary endpoint, CV death and HF hospitalization, and the second family consisted of total HF hospitalizations, time to the first of all-cause mortality or HF hospitalization, and all-cause mortality. Secondary endpoints in the first family were tested because the primary composite endpoint was significant. Secondary endpoints in the second family were tested according to a hierarchical testing procedure to control the family wise type I error rate.

5.3. Results of Analyses of Clinical Trials/Studies Intended to Demonstrate Benefit to Patients

5.3.1. Baseline Demographics

Baseline demographics were similar in the two treatment groups (Table 4). The mean age was 67 years (range 23 to 98) with 14% of subjects aged > 80 years old. The majority of subjects were male (76%). Overall, 64% of subjects were white, 22% Asian, and 5% black. Sites in the United States contributed 8% of subject enrollment.

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Table 4. Baseline Demographic Characteristics, ITT Population, VICTORIA

	Vericiguat (N=2526)	Placebo (N=2524)	Total (N=5050)
Male	1921 (76.0)	1921 (76.1)	3842 (76.1)
Age			
Mean (SD)	67.5 (12.2)	67.2 (12.2)	67.3 (12.2)
Median (Min, Max)	69.0 (24, 98)	68.0 (23, 97)	69.0 (23, 98)
Age			
<=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)	1511 (29.9)
71 to 80	737 (29.2)	778 (30.8)	1515 (30.0)
>=81	362 (14.3)	319 (12.6)	681 (13.5)
Race			
White	1621 (64.2)	1618 (64.1)	3239 (64.1)
Asian	571 (22.6)	561 (22.2)	1132 (22.4)
Multiple	183 (7.2)	180 (7.1)	363 (7.2)
Black[1]	123 (4.9)	126 (5.0)	249 (4.9)
American Indian or Alaska native	24 (1.0)	28 (1.1)	52 (1.0)
Native Hawaiian or Pacific Islander	3 (0.1)	11 (0.4)	14 (0.3)
Ethnicity			
Hispanic or Latino	410 (16.2)	403 (16.0)	813 (16.1)
Not Hispanic or Latino	2044 (80.9)	2065 (81.8)	4109 (81.4)
Region[2]			
Eastern Europe	848 (33.6)	846 (33.5)	1694 (33.5)
Asia Pacific	592 (23.4)	591 (23.4)	1183 (23.4)
Western Europe	443 (17.5)	446 (17.7)	889 (17.6)
Latin and South America	362 (14.3)	362 (14.3)	724 (14.3)
North America	281 (11.1)	279 (11.1)	560 (11.1)
United States	208 (8.2)	207 (8.2)	415 (8.2)

[1] Enrollment region: 120 (48%) North America, 111 (45%) Eastern Europe.
[2] Eastern Europe: Czech Republic, Greece, Hungary, Israel, Poland, Russian Federation, South Africa, Turkey, Ukraine; Asia Pacific: Australia, China, Hong Kong, Japan, Korea, Malaysia, New Zealand, Philippines, Singapore, Taiwan; Western Europe: Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, United Kingdom; Latin and South America: Argentina, Chile, Colombia, Guatemala, Mexico, Peru, Puerto Rico; North America: Canada, United States
Source: Reviewer's table, dataset: adsl and OCS Analysis Studio, Custom Table Tool

Baseline clinical characteristics were well balanced between the treatment groups (Table 5). At screening, the mean LVEF was 29%. Approximately half of subjects had an LVEF < 30%. At randomization, 99% of subjects were categorized as NYHA Class II or Class III and the median NT-proBNP level was 2816 pg/mL (Range 0 to > 175000 pg/mL). Approximately two-thirds of subjects enrolled within 3 months of a HF hospitalization index event. The median time from any index event to randomization was 32 days.

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Table 5 Baseline Clinical Characteristics, ITT Population, VICTORIA

	Vericiguat (N=2526)	Placebo (N=2524)	Total (N=5050)
NYHA Class at Randomization			
I	0	2 (0.1)	2 (0.0)
II	1478 (58.5)	1497 (59.3)	2975 (58.9)
III	1010 (40.0)	993 (39.3)	2003 (39.7)
IV	35 (1.4)	31 (1.2)	66 (1.3)
LFEF at Screening			
Mean (SD)	29.0 (8.26)	28.8 (8.34)	28.9 (8.30)
Median (Min, Max)	30.0 (6, 45)	29.0 (5, 45)	30.0 (5, 45)
<15%	69 (2.7)	73 (2.9)	142 (2.8)
15% to <20%	227 (9.0)	227 (9.0)	454 (9.0)
20% to <25%	425 (16.8)	451 (17.9)	876 (17.3)
25% to <30%	489 (19.4)	529 (21.0)	1018 (20.2)
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)
NT-proBNP at Randomization			
Q1 (<=1556)	599 (23.7)	604 (23.9)	1203 (23.8)
Q2 (1557 - 2816)	613 (24.3)	589 (23.3)	1202 (23.8)
Q3 (2817 - 5314)	586 (23.2)	613 (24.3)	1199 (23.7)
Q4 (>5314)	616 (24.4)	585 (23.2)	1201 (23.8)
Index event			
HF hospitalization 3-6 months	454 (18.0)	417 (16.5)	871 (17.2)
HF hospitalization within 3 months	1673 (66.2)	1705 (67.6)	3378 (66.9)
IV diuretic for HF (without hospitalization) within 3 months	399 (15.8)	402 (15.9)	801 (15.9)
Time from index event to randomization			
Mean (SD)	50.9 (46.08)	49.5 (47.05)	50.2 (46.57)
Median (Min, Max)	33.0 (2, 343)	31.0 (2, 621)	32.0 (2, 621)
HF Etiology[1]			
Ischemic	1657 (65.6)	1586 (62.8)	3243 (64.2)
eGFR (mL/min/1.73m^2) at Randomization			
<=30	259 (10.3)	247 (9.8)	506 (10.0)
>30 to <=60	1054 (41.7)	1064 (42.2)	2118 (41.9)
>60	1161 (46.0)	1174 (46.5)	2335 (46.2)

[1] Data on HF etiology was not recorded by Investigators on the eCRF. Subjects with ischemic HF etiology defined as any subject with 1 or more of the following reported medical conditions: coronary artery disease, myocardial infarction, coronary artery bypass graft or percutaneous coronary intervention
Source: Reviewer's table, dataset: adsl and adbase, OCS Analysis Studio, Custom Table Tool

Reviewer's Comment: VICTORIA was designed to study "high risk" patients with chronic HFrEF with entry criteria including a previous HF decompensation and an elevated NT-proBNP level. A higher percent of subjects in VICTORIA (41%) were either NYHA Class III or IV, as compared with 25% and 32% of the subjects, respectively, in the two other contemporary HFrEF trials – PARADIGM-HF (sacubitril/valsartan) and the DAPA-HF (dapagliflozin). Similarly, the median NT-proBNP value was < 1700 pg/mL in PARADIGM-HF and DAPA-HF as compared with 2816 pg/mL in VICTORIA.

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Per the VICTORIA study protocol, all subjects were expected to receive standard of care for HF treatment based on locally relevant guidelines. At baseline, the reported standard of care therapies were well-balanced between the treatment groups, as shown in Table 6. Overall, 93% of subjects were taking a beta-blocker, 73% were taking ACEi or ARB, 70% were on MRA, and 15% were on sacubitril/valsartan at baseline. About 60% of subject were treated with all three standard of care therapies for HF (beta-blocker, RAS inhibitor, or MRA). Overall, 32% of subjects had cardiac device therapies such as an ICD or biventricular pacemaker.

Table 6 Baseline Use of Standard of Care for Heart Failure, ITT Population, VICTORIA

	Vericiguat (N=2526)	Placebo (N=2524)	Total (N=5050)
Baseline Standard of Care Medications			
ACE-I or ARB	1847 (73.1)	1853 (73.4)	3700 (73.3)
Beta blocker	2349 (93.0)	2342 (92.8)	4691 (92.9)
MRA	1747 (69.2)	1798 (71.2)	3545 (70.2)
Sacubitril/valsartan	360 (14.3)	371 (14.7)	731 (14.5)
Triple therapy[1]	1479 (58.6)	1528 (60.5)	3007 (59.5)
Baseline Standard of Care Devices			
ICD	696 (27.6)	703 (27.9)	1399 (27.7)
Biventricular pacemaker	370 (14.6)	369 (14.6)	739 (14.6)
Device[2]	813 (32.2)	802 (31.8)	1615 (32.0)

[1] Beta blocker, MRA and any RAS inhibitor
[2] Subjects who had an ICD and/or biventricular pacemaker at baseline
Source: Reviewer's table, dataset: adsl and adsoch, OCS Analysis Studio, Custom Table Tool
Abbreviations: N, number of subjects in treatment group; ACE-I, Angiotensin-converting enzyme inhibitor, ARB, Angiotensin receptor blocker, MRA, Mineralocorticoid receptor antagonist, ICD, Implantable cardioverter-defibrillators

There was regional variability in use of HF treatments (Table 7). A higher proportion of subjects in regions outside North America were receiving MRAs at baseline compared with subjects in North America. Use of sacubitril/valsartan at baseline was reported for 26%, 25% and 18% in North American, Western Europe and Asia Pacific, respectively compared with less than 9% in other regions. North America and Western Europe also had a higher portion of subjects who were treated with ICDs and biventricular pacemakers compared to other regions. These regional differences in the use of standard care of therapies for HF persisted throughout the course of the study.

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Table 7 Baseline Use of Standard of Care for Heart Failure by Region, ITT Population, VICTORIA

	Asia Pacific (N=1183)	Eastern Europe (N=1694)	Latin and South America (N=724)	North America (N=560)	Western Europe (N=889)
ACE or ARB	841 (71.1)	1393 (82.2)	607 (83.8)	311 (55.5)	548 (61.6)
Beta blocker	1056 (89.3)	1611 (95.1)	668 (92.3)	530 (94.6)	826 (92.9)
MRA	804 (68.0)	1322 (78.0)	583 (80.5)	287 (51.2)	549 (61.8)
Sacubitril/valsartan	212 (17.9)	87 (5.1)	64 (8.8)	147 (26.2)	221 (24.9)
Triple therapy[1]	660 (55.8)	1135 (67.0)	508 (70.2)	238 (42.5)	466 (52.4)
ICD	178 (15.0)	454 (26.8)	81 (11.2)	299 (53.4)	387 (43.5)
Biventricular pacemaker	125 (10.6)	218 (12.9)	46 (6.4)	147 (26.2)	203 (22.8)
Device[2]	230 (19.4)	507 (29.9)	111 (15.3)	320 (57.1)	447 (50.3)

[1] Beta blocker, MRA and any RAS inhibitor
[2] Subjects who had an ICD and/or biventricular pacemaker at baseline
Source: Reviewer's table, dataset: adsl and adsoch, OCS Analysis Studio, Custom Table Tool
Abbreviations: N, number of subjects in treatment group; ACE-I, Angiotensin-converting enzyme inhibitor, ARB, Angiotensin receptor blocker, MRA, Mineralocorticoid receptor antagonist, ICD, Implantable cardioverter-defibrillators

5.3.2. Disposition

Of 6,857 screened subjects, 5,050 (74%) were randomized (Table 8). All non-randomized subjects were screen failures. The primary reason for screen failure was not meeting required BNP or NT-proBNP level (60%).

Table 8. Patient Screening and Randomization, VICTORIA

Disposition	VICTORIA
No. patients screened	6857 (100%)
No. of patients not randomized	1807 (26%)
No. of screening failures	1807[1] (26%)
No. of patients randomized	5050 (74%)

[1]1805 was due to inclusion/exclusion criteria and two patients did not have a specific reason for screen failure.
Source: Study Report Figure 10-1

A total of 5,050 subjects were randomized, 2,524 to placebo (50%) and 2,526 (50%) to vericiguat (Table 9). All but 16 subjects (0.3%) received at least 1 dose of study medication. At the last visit, 62% of subjects were alive and completed the study on study medication. The proportions of subjects who discontinued treatment were similar in both treatment groups. Death was the most common reason for discontinuation. As of the primary completion date (18 Jun 2019), almost all randomized subjects had completed follow-up for the primary endpoint (99.5% and 99.6% in the placebo and vericiguat groups, respectively). The median durations of follow-up for the primary endpoint were 10.4 and 11.1 months for the placebo and vericiguat groups, respectively.

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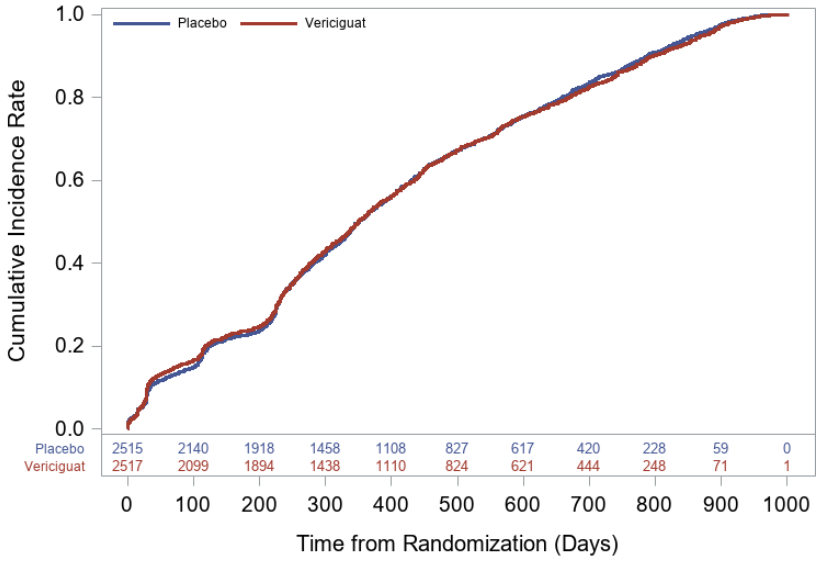
Table 9 Patient Disposition, ITT Population, VICTORIA

	Vericiguat (N=2526)	Placebo (N=2524)
Randomized	2526 (100)	2524 (100)
Not Treated	7(0.3)	9 (0.4)
Status for Study Medication in Trial		
Completed	1547 (61.4)	1561 (62.1)
Discontinued	973 (38.5)	957 (37.9)
Adverse event	177 (7.0)	160 (6.3)
Death	358 (14.2)	386 (15.3)
Lost to follow-up	9 (0.4)	11 (0.4)
Non-compliance with study drug	49 (1.9)	49 (1.9)
Physician decision	176 (7.0)	158 (6.3)
Protocol deviation	8 (0.3)	2 (0.1)
Withdrawal by subject	196 (7.8)	191 (7.6)
Status and Amount of Follow-up for the Primary Endpoint[1]		
Complete follow-up for Primary Endpoint	2515 (99.6%)	2511 (99.5%)
Mean (SD) length of follow-up (months)[2]	12.7 (8.4)	12.2 (8.4)
Median (Q1, Q3) length of follow-up (months)	11.1 (6.5, 19.1)	10.4 (6.1, 18.7)

[1] As of the primary completion date (18 Jun 2019)
[2] Follow-up time for each subject was computed 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 data (18 Jun 2019)
Source: Reviewer's table, dataset: adsl, adbase and ds, CSR Figure 10-1,OCS Analysis Studio, Custom Table Tool

As an assessment of adequacy of follow-up, Figure 2 shows the time to the last follow-up, defined as the last clinic visit at which a pulse was recorded. The number of days of follow-up are similar in the two treatment groups.

Figure 2 Days of Follow Up Based on Pulse Data, ITT Population, VICTORIA



Source: Reviewer's figure, dataset: advs

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5.3.3. Protocol Deviation

The proportions of subjects with protocol deviations, overall and by category, were similar between the treatment groups (Table 10). The most common protocol deviations in both groups involved safety reporting (i.e., reportable safety events and/or follow up safety event information that were not reported per the timeline outlined in the protocol) and inclusion/exclusion criteria. No subject's data were excluded from the primary analyses due to protocol deviation.

Table 10 Summary of Important Protocol Deviation, ITT Population, VICTORIA

	Vericiguat (N=2526)	Placebo (N=2524)	Total (N=5050)
One or more important protocol deviations	463 (18.3)	435 (17.2)	898 (17.8)
Safety reporting	212 (8.4)	191 (7.6)	403 (8.0)
Inclusion/ exclusion criteria	173 (6.8)	139 (5.5)	312 (6.2)
Prohibited medications	69 (2.7)	102 (4.0)	171 (3.4)
Trial procedures	33 (1.3)	37 (1.5)	70 (1.4)
Study intervention	24 (1.0)	25 (1.0)	49 (1.0)
Informed consent form missing	5 (0.2)	12 (0.5)	17 (0.3)

Source: Reviewer's table, dataset: adsl, DV, OCS Analysis Studio, Custom Table Tool

5.3.4. Analysis of Primary Endpoint

In the vericiguat group, 2,526 patients were randomized, 2,519 were treated, and 2,515 completed follow-up for the primary endpoint. In the placebo group, 2,524 patients were randomized, 2,515 were treated, and 2,511 completed follow-up for the primary endpoint.

Of the 1,046 investigator-reported deaths, 856 were reported as CV death, and 93.8% were confirmed by the CEC. After CEC review of investigator-reported non-CV deaths, an additional 52 events were categorized as CV deaths. Overall, 74.9% of all investigator-reported HF hospitalizations were confirmed by the CEC. After CEC review of all other investigator reported hospitalization endpoint events, an additional 59 events were deemed to be HF hospitalizations by the CEC.

Vericiguat treatment resulted in a (mean) 10% relative hazard reduction in the first event of CEC confirmed CV death or HF hospitalization compared with placebo (HR: 0.90; 95% CI: 0.82-0.98; $p = 0.019$) which was statistically significant. The treatment effect became evidence at 3 to 4 months and persisted throughout the study (Figure 3). Over the course of the study, the annualized absolute risk reduction was 4.2% with vericiguat relative to placebo.

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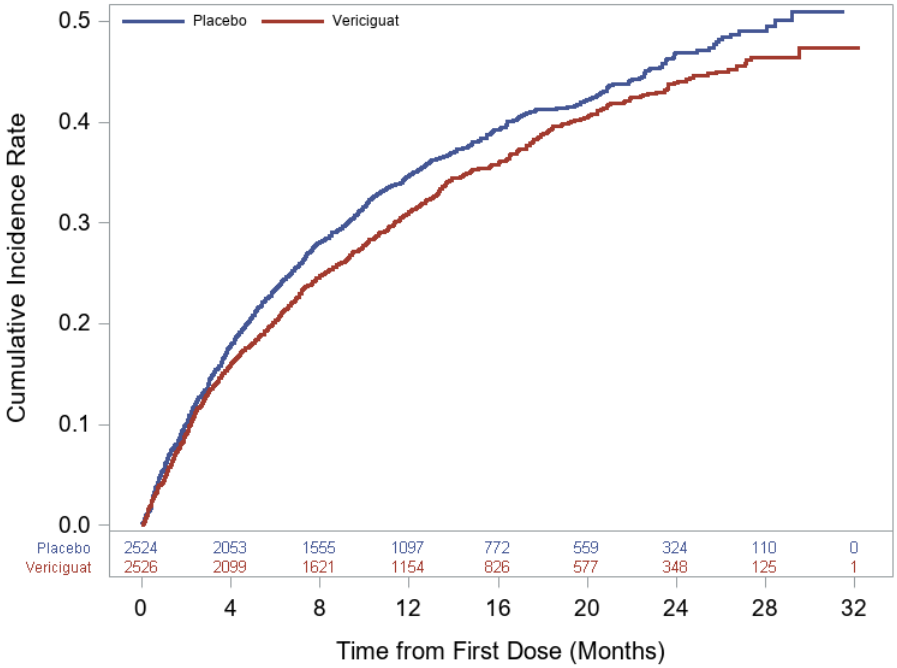
Table 11 Results for the Primary Efficacy Endpoint, ITT Population, VICTORIA

	Vericiguat (N= 2526)		Placebo (N = 2524)		Vericiguat vs. Placebo	
	n (%)	ER[a]	n (%)	ER[a]	HR (95% CI)	*p* value
Primary composite endpoint	897 (35.5)	33.6	972 (38.5)	37.8	0.90 (0.82, 0.98)	0.019
Heart failure hospitalization	691 (27.4)		747 (29.6)			
CV death	206 (8.2)		225 (8.9)			

[a] Annualized event rate per 100 subject-years
Source: Reviewer's table, dataset: adsl and adttec

Figure 3 Kaplan-Meier Plot for First Primary Endpoint, ITT Population, VICTORIA



Source: Reviewer's figure, dataset: adsl and adttec

Sensitivity Analyses

The applicant conducted the following sensitivity analyses of the primary efficacy endpoint including analyses of:

- On-treatment occurrence of primary endpoint events, defined as events occurring up to 14 days after study drug discontinuation
- All events up to the last study visit

Additional sensitivity analyses of the primary efficacy endpoint were evaluated including analyses of:

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- Investigator-reported events, both CEC confirmed and non-confirmed up to the primary completion date
- A per-protocol set excluding 78 placebo and 121 vericiguat subjects who had protocol deviations for not meeting required entry criteria for NYHA Class, LVEF, NT-proBNP or worsened HF event.

The treatment effect was generally maintained in all sensitivity analyses (Table 12).

Table 12 Sensitivity Analyses for the Primary Endpoint, ITT Population, VICTORIA

	Vericiguat (N=2526)	Placebo (N=2524)	Hazard Ratio (95% CI; 2 sided p-value)
Data up to the primary completion date			
Investigator-reported events	1016 (40.2)	1077 (42.7)	0.92 (0.84, 1.00; 0.04)
On treatment events[1]	735 (29.2)	801 (31.8)	0.91 (0.82, 1.01; 0.06)
Per-protocol set[2]	864 (35.9)	941 (38.5)	0.91 (0.83, 1.00; 0.05)
All data through last study visit			
All events through last study visit (ITT population)	938 (33.4)	1002 (39.7)	0.91 (0.83, 0.99; 0.04)

1. Excluded subjects who did not start treatment (n = 7 and 9 in the vericiguat and placebo group, respectively) and included events that occurred within 14 days after the last dose of study drug
2. Excluded subjects who did not meet the inclusion criteria (n = 121 and 78 in the vericiguat and placebo group, respectively)

Source: Reviewer's table, dataset: adsl, adttec, and DV

Pre-specified Subgroup Analyses

Subgroup analyses were performed for the primary efficacy endpoint for age, sex, race, geographic region and other important clinical characteristics, as depicted in Figure 4. The effect of vericiguat relative to placebo was generally consistent across the prespecified subgroups except for 2 subgroup factors: age group 2 (< 75 years vs. ≥ 75 years) and NT-proBNP at baseline by quartiles, for which the interaction p-values were < 0.05 for both. The observed HR was higher for age ≥ 75 years compared with age < 75 years and was higher in the fourth quartile of baseline NT-proBNP compared to the lower 3 quartiles. See Section 5.3.5.1 and 5.4.2 for more discussions on these subgroup findings.

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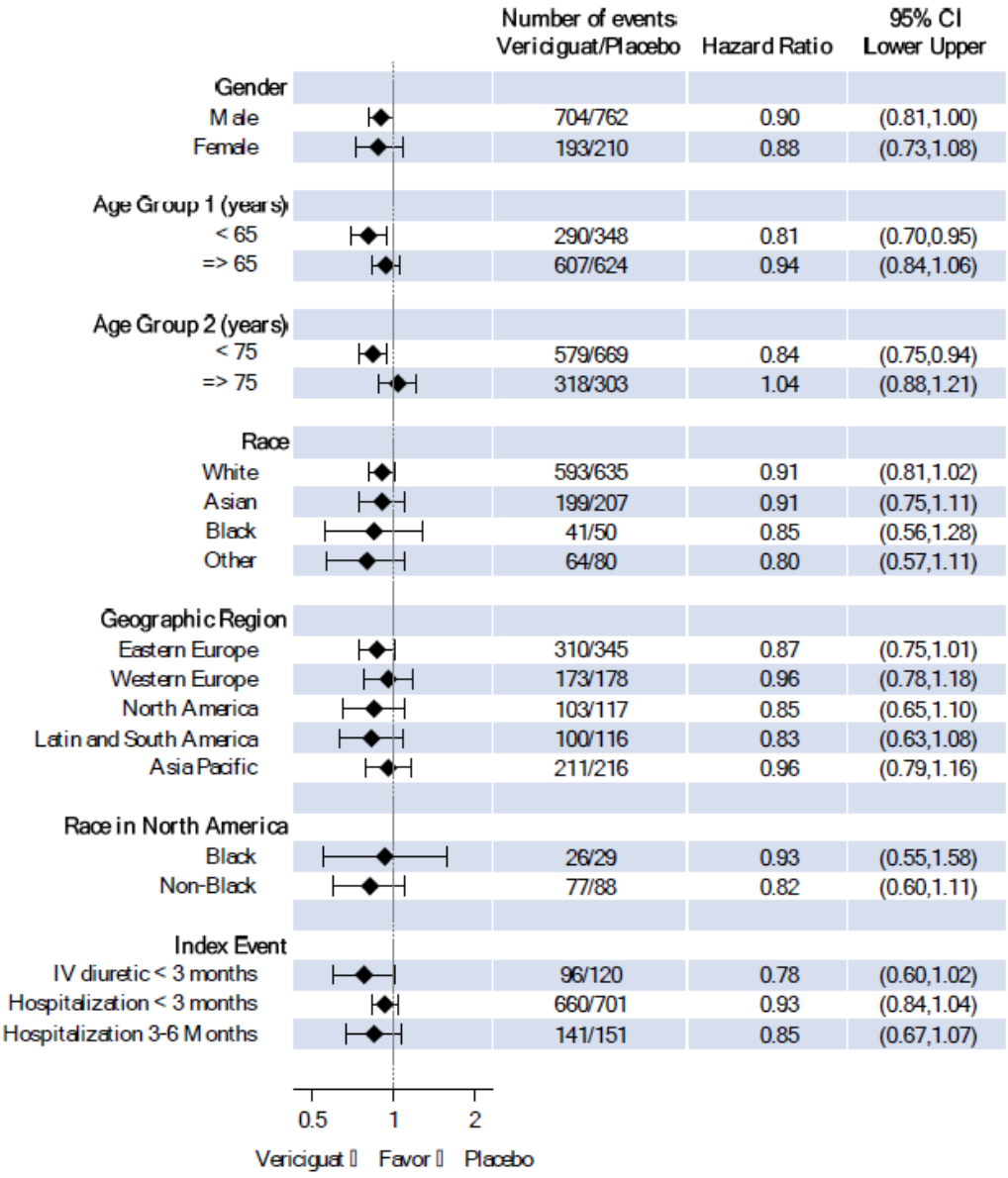
Figure 4 Subgroup Analyses for the Primary Composite Endpoint: Time to the First Event of CEC Confirmed CV Death or HF Hospitalization, ITT Population, VICTORIA



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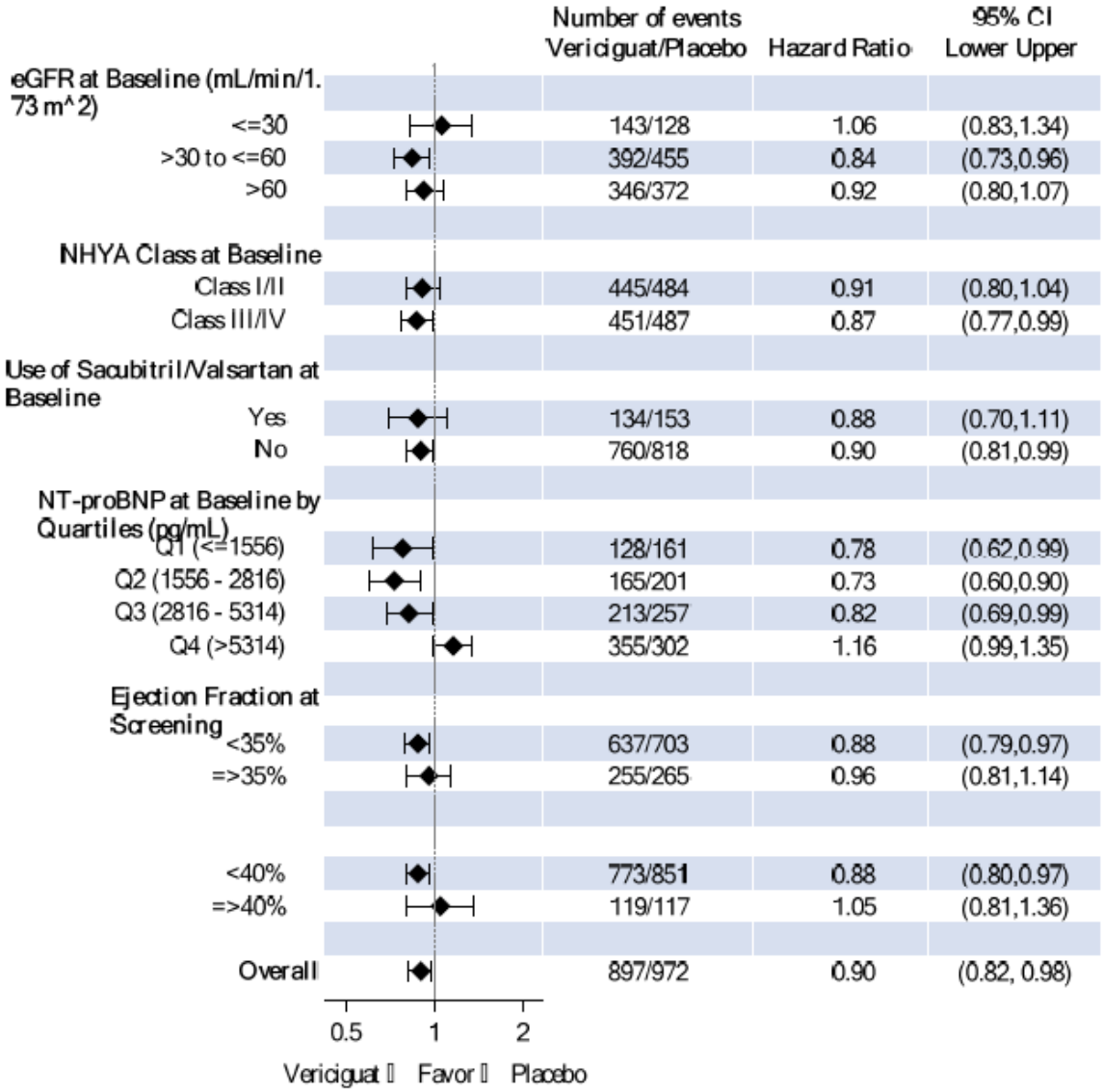

Source: The applicant's CSR, Figure 11-2

Post Hoc Subgroup Analyses

Post hoc subgroup analyses were conducted for several subgroups of interest including standard of care at baseline, use of ivabradine at baseline, baseline LVEF (quartile) and baseline SBP (Table 13). In general, the results for the primary efficacy endpoint were consistent across these subgroups.

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Table 13 Post Hoc Subgroup Analyses for The Primary Composite Endpoint: Time to The First Event of CEC Confirmed CV Death or HF Hospitalization, ITT Population, VICTORIA

Subgroup		% of population	Event Rate (per 100 pt-yrs)		Hazard Ratio (Vericiguat vs. Placebo)	95% CI
			Vericiguat	Placebo		
Triple therapy[1]	No	40.4	40.8	43.2	0.95	(0.83, 1.09)
	Yes	59.6	28.9	34.4	0.85	(0.75, 0.96)
ICD	No	72.1	31.6	34.5	0.92	(0.82, 1.03)
	Yes	27.7	38.7	47.0	0.85	(0.72, 0.99)
Biventricular pacemaker	No	85.2	33.2	36.4	0.91	(0.83, 1.01)
	Yes	14.6	35.7	46.8	0.80	(0.64, 1.01)
Use of ivabradine	No	93.4	33.3	37.3	0.90	(0.82, 0.99)
	Yes	6.6	37.9	45.1	0.90	(0.64, 1.26)
Baseline LVEF By quartiles (%)	Q1 (≤23)	27.2	37.1	46.8	0.82	(0.70, 0.97)
	Q2 (24-29)	22.1	32.2	38.6	0.86	(0.71, 1.05)
	Q3 (30-35)	27.2	35.2	35.4	0.98	(0.83, 1.17)
	Q4 (≥36)	23.2	29.0	29.9	0.96	(0.79, 1.18)
Baseline SBP by quartiles (mmHg)	Q1 (< 109)	24.1	40.9	48.5	0.85	(0.72, 1.01)
	Q2 (109 - <119)	25.5	31.8	39.6	0.81	(0.67, 0.97)
	Q3 (119 - <131)	24.3	29.6	32.1	0.93	(0.77, 1.13)
	Q4 (≥ 131)	25.7	32.7	32.9	0.99	(0.83, 1.19)

[1] Beta blocker, MRA and any RAS inhibitor
Source: Reviewer's table, dataset: adsl, adsoch, adbase, advs and adttec

5.3.5. Analysis of Secondary Endpoints

5.3.5.1. Components of the Primary Efficacy Endpoint

Vericiguat-treated subjects experienced fewer first HF hospitalizations and CV deaths, with only HF hospitalization achieving statistical significance (Table 14). Similar results were found for the investigator-reported events. The Kaplan-Meier curves separated at around 4 months for the first HF hospitalization and the treatment effect persisted for the duration of the trial (Figure 5). There was no difference between the treatment groups for the Kaplan-Meier curves for CV death (Figure 6).

Table 14 Results for The Total Cardiovascular Deaths and First Heart Failure Hospitalization, ITT Population, VICTORIA

		Vericiguat (N= 2526)	Placebo (N=2524)	HR (95% CI)	*p*-value
Adjudicated	HF Hospitalization	691 (27.4)	747 (29.6)	0.90 (0.81, 1.00)	0.048

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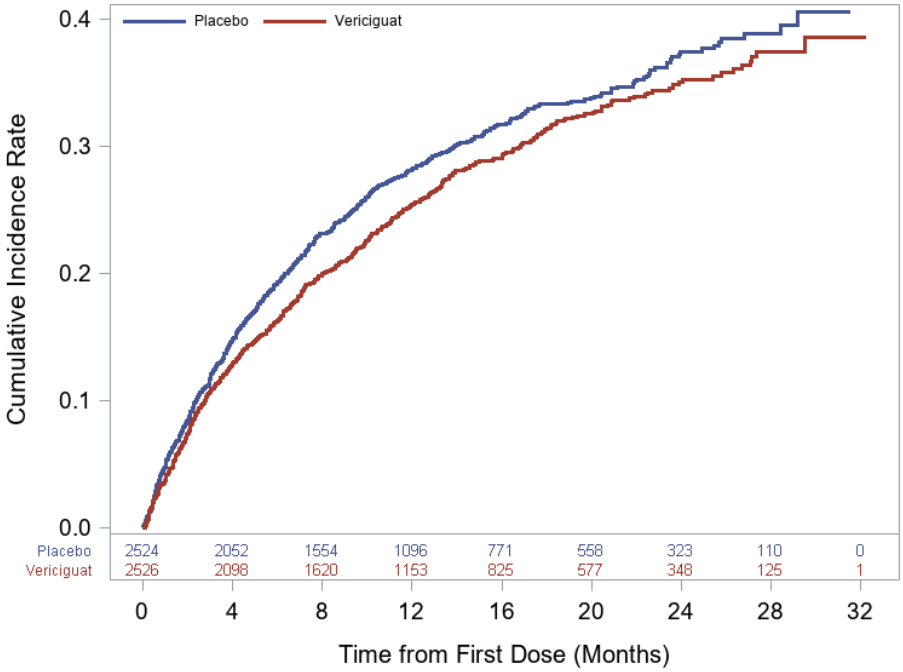
	CV Death	414 (16.4)	441 (17.5)	0.93 (0.81, 1.06)	0.269
Investigator-reported	HF Hospitalization	831 (32.9)	901 (35.7)	0.90 (0.82, 0.99)	0.023
	CV Death	419 (16.6)	437 (17.3)	0.95 (0.83, 1.08)	0.427

Source: Reviewer's table, dataset: adsl and adttec

Reviewer's Comment: Both components of the primary efficacy endpoint trended to favoring vericiguat.

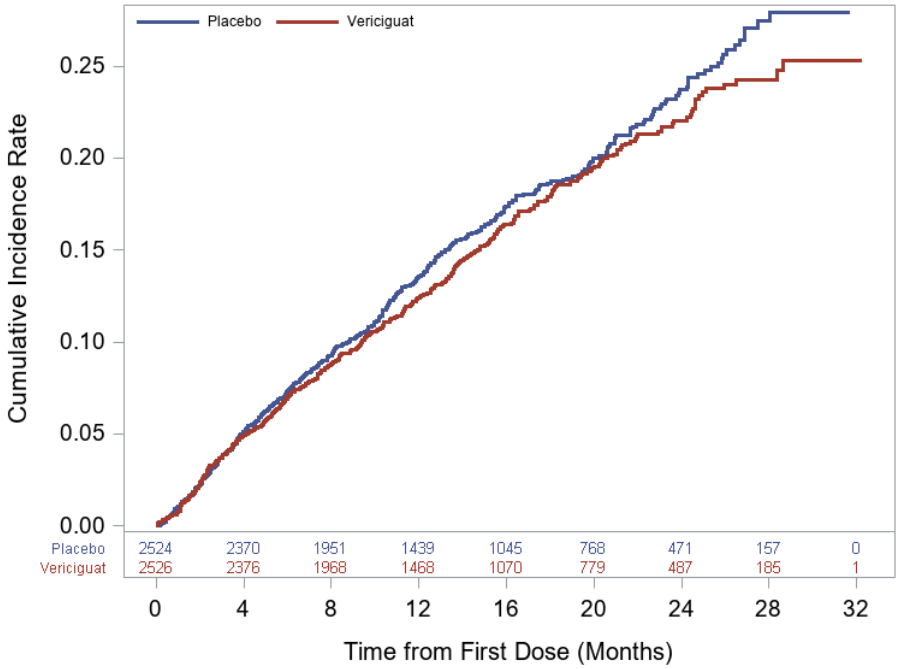
Figure 5 Kaplan-Meier Plot for First Hospitalization for Heart Failure, ITT Population, VICTORIA



Source: Reviewer's figure, dataset: adsl and adttec

Reference ID: 4733225

Figure 6 Kaplan-Meier Plot for CV Death, ITT Population, VICTORIA



Source: Reviewer's figure, dataset: adsl and adttec

The incidence and type of CV death were similar between the two treatment groups (Table 15).

Table 15 Causes of Cardiovascular Death, ITT Population, VICTORIA

	Vericiguat (N=2526)	Placebo (N=2524)
CV Death	414 (16.4)	441 (17.5)
Heart failure	165 (6.5)	191 (7.6)
Undetermined cause of death	112 (4.4)	101 (4.0)
Sudden cardiac death	107 (4.2)	113 (4.5)
Other cardiovascular event	13 (0.5)	9 (0.4)
Myocardial infarction	10 (0.4)	11 (0.4)
Stroke	7 (0.3)	16 (0.6)

Source: Reviewer's table, dataset: adsl and DV, OCS Analysis Studio, Custom Table Tool

Subgroup Analyses

Similar to the primary efficacy endpoint, the subgroup results for the components of the primary endpoint were generally consistent across the prespecified subgroups (see Appendix III.12.1 and III.12.2). Age and baseline NT-proBNP were two subgroups with interaction *p*-values < 0.05 for the primary efficacy endpoint. The subgroup results by these two factors for both first HF hospitalization and CV death are summarized in the tables below.

Reference ID: 4733225

Table 16 The First HF Hospitalization within Age and NT-proBNP Subgroups, ITT Population, VICTORIA

Subgroup		% of population	Event Rate (per 100 pt-yrs)		Hazard Ratio (Vericiguat vs. Placebo)	95% CI
			Vericiguat	Placebo		
Age group 1 (years)	< 65	37.1	22.2	29.2	0.77	(0.64, 0.92)
	≥ 65	62.9	28.1	29.0	0.97	(0.85, 1.10)
Age group 2 (years)	< 75	69.0	24.1	29.0	0.84	(0.74, 0.95)
	≥ 75	31.0	30.1	29.3	1.04	(0.87, 1.25)
NT-proBNP (pg/mL)	Q1 (≤ 1556)	23.8	14.3	19.6	0.74	(0.57, 0.95)
	Q2 (1556 - 2816)	23.8	18.4	24.4	0.76	(0.61, 0.96)
	Q3 (2816 - 5314)	23.7	27.7	35.0	0.80	(0.65, 0.98)
	Q4 (> 5314)	23.8	52.0	44.0	1.19	(0.99, 1.44)

Source: Reviewer's table, dataset: adsl, adbase and adttec

Table 17 CV Death within Age and NT-proBNP Subgroups, ITT Population, VICTORIA

Subgroup		% of population	Event Rate (per 100 pt-yrs)		Hazard Ratio (Vericiguat vs. Placebo)	95% CI
			Vericiguat	Placebo		
Age group 1 (years)	< 65	37.1	10.7	11.8	0.90	(0.71, 1.14)
	≥ 65	62.9	14.2	15.2	0.93	(0.79, 1.10)
Age group 2 (years)	< 75	69.0	11.4	13.7	0.83	(0.70, 0.98)
	≥ 75	31.0	16.2	14.4	1.12	(0.89, 1.40)
NT-proBNP (pg/mL)	Q1 (≤ 1556)	23.8	4.07	5.55	0.75	(0.48, 1.16)
	Q2 (1556 - 2816)	23.8	7.61	10.1	0.76	(0.55, 1.06)
	Q3 (2816 - 5314)	23.7	12.5	15.3	0.83	(0.63, 1.09)
	Q4 (> 5314)	23.8	32.0	27.1	1.16	(0.95, 1.43)

Source: Reviewer's table, dataset: adsl, adbase and adttec

Reviewer's Comment: Unfavorable efficacy results in subjects in the highest baseline NT-proBNP quartile were observed for both components of the primary efficacy endpoint. See Section 5.4.2 for more discussions on this subgroup finding. Differential treatment effects by age groups were mainly observed for CV mortality; however, this interaction effect was no longer significant after adjusting for other factors in a multivariate mode, which suggests that the treatment effect is similar across age groups (see Section 5.4.2).

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The *post hoc* subgroup analysis by standard of care at baseline for the first HF hospitalization and CV death are summarized in the tables below. There were no differences with respect to HR for HF hospitalization by standard of care (i.e., either HF medication or device) (Table 18). There was a significant interaction *p*-value for CV mortality by device use at baseline. Specifically, vericiguat-treated subjects with device use at baseline had lower CV mortality compared to the placebo-treated subjects. In contrast, HR was close or greater than 1 among subjects without a device at baseline. See Section 5.4.1 for discussions on this subgroup finding and the related review issues.

Table 18 First HF Hospitalization by Standard of Care for HF treatment at Baseline, ITT Population, VICTORIA

Subgroup		% of population	Event Rate (per 100 pt-yrs)		Hazard Ratio (Vericiguat vs. Placebo)	95% CI
			Vericiguat	Placebo		
Triple Therapy	No	40.5	30.7	32.9	0.93	(0.80, 1.09)
	Yes	59.5	22.7	26.6	0.87	(0.75, 1.00)
ICD	No	72.1	22.6	26.0	0.87	(0.77, 0.99)
	Yes	27.7	34.2	37.4	0.95	(0.79, 1.12)
Biventricular Pacemaker	No	85.2	25.2	27.9	0.91	(0.81, 1.01)
	Yes	14.6	29.8	36.3	0.88	(0.68, 1.13)

Source: Reviewer's table, dataset: adsl, adsoch and adttec

Table 19 CV Death by Standard of Care for HF treatment at Baseline, ITT Population, VICTORIA

Subgroup		% of population	Event Rate (per 100 pt-yrs)		Hazard Ratio (Vericiguat vs. Placebo)	95% CI
			Vericiguat	Placebo		
Triple Therapy	No	40.5	16.7	16.1	1.05	(0.87, 1.27)
	Yes	59.5	10.3	12.5	0.82	(0.68, 0.98)
ICD[a]	No	72.1	13.1	12.4	1.06	(0.90, 1.24)
	Yes	27.7	12.3	17.8	0.69	(0.55, 0.88)
Biventricular Pacemaker[b]	No	85.2	12.8	12.9	0.99	(0.85, 1.15)
	Yes	14.6	13.1	20.3	0.65	(0.47, 0.90)

a The interaction *p*-value is 0.0046
b The interaction *p*-value is 0.025

Source: Reviewer's table, dataset: adsl, adsoch and adttec

5.3.5.2. Other Secondary Endpoints

Because the primary efficacy endpoint was successful, the secondary endpoints except the components of the primary efficacy endpoint were tested using a hierarchical testing approach for controlling multiplicity. Results of these secondary endpoints are shown in Table 20.

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Vericiguat treated subjects had favorable outcomes with regard to time to total hospitalization and the composite endpoint of all-cause mortality or HF hospitalization (p <0.05). There was no difference between groups in all-cause mortality.

Table 20 Results for The Secondary Endpoints, ITT Population, VICTORIA

	Vericiguat (N= 2526)	Placebo (N=2524)	HR (95% CI)	*p*-value
Total HF hospitalization[1] (first and recurrence)	1223 (48.4)	1336 (52.9)	0.91 (0.84, 0.99)	0.023
All-cause mortality or HF hospitalization	957 (37.9)	1032 (40.9)	0.90 (0.83, 0.98)	0.021
All-cause mortality	512 (20.4)	534 (21.2)	0.95 (0.84, 1.07)	0.378

1. Hazard ratio for total HF hospitalization was calculated based on Andersen-Gill model. Robust standard errors are used to account for correlations of event times within a subject

Source: Reviewer's table, dataset: adsl and adttec.

5.3.6. Exploratory Analyses

The applicant conducted several supportive exploratory analyses to further evaluate the efficacy of vericiguat. These analyses were not adjusted for multiplicity; therefore, the results should be interpreted with caution.

5.3.6.1. Heart Failure Hospitalization or Urgent Heart Failure Visit

Vericiguat treated subjects had lower rate of the composite of HF hospitalization and urgent heart failure visit than placebo (Table 21). Of note, 74.9% of all investigator-reported HF hospitalizations and 46.8% of the investigator-reported urgent HF visit were confirmed by the CEC.

Table 21 Results for The Exploratory Composite of HF Hospitalization and Urgent Heart Failure Visit, ITT Population, VICTORIA

	Vericiguat (N= 2526)	Placebo (N=2524)	HR (95% CI)	*p*-value
Exploratory composite of HF hospitalization and urgent heart failure visit	730 (28.9)	795 (31.5)	0.89 (0.81, 0.99)	0.030

Source: Reviewer's table, dataset: adsl and adttec.

5.3.6.2. Number of Days Alive and not Hospitalization for Heart Failure

There was no difference between the treatment groups in mean number of days alive and not hospitalized for HF. The average days alive outside of HF hospitalization were 455.6 days and 449.5 days in the vericiguat and placebo group, respectively (p-value = 0.37) (Table 22).

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Table 22 Number of Days Alive Outside of HF Hospitalization, ITT Population, VICTORIA

	Vericiguat			Placebo			Difference in LS Means†	95% CI†	p-Value†
	N	Mean (SD)	LS Mean†	N	Mean (SD)	LS Mean†			
Days Alive Outside of CEC Confirmed Heart Failure Hospitalization	2526	455.6 (243.64)	457.59	2524	449.5 (240.74)	451.47	6.11	(-7.15, 19.38)	0.366

† Based on an ANOVA model with study group and stratification factors as covariates.
SD=Standard Deviation, LS = least Squares, ANOVA = Analysis of Covariance, CI = Confidence Interval
Based on data up to the primary completion date (18Jun2019).

Source: CSR Table 11-14

5.3.6.3. Health-related Quality of Life Measures

There was no difference between the treatment groups in health-related quality of life measures. The KCCQ Overall Summary Score and the EQ-5D-5L UK Index Score from baseline to Week 32 were similar in subjects treated with vericiguat and placebo.

Table 23 Analysis of Change from Baseline in KCCQ: Overall Summary Score at Week 32, ITT Population, VICTORIA

	Baseline		Week 32		Change from Baseline at Week 32		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI†)
Vericiguat	2248	58.7 (22.9)	1913	61.1 (31.4)	1758	2.6 (28.4)	2.3 (1.1, 3.5)
Placebo	2222	58.9 (22.4)	1890	59.8 (32.1)	1716	0.8 (30.0)	1.1 (-0.1, 2.3)
Treatment Comparison					Difference in LS Means (95% CI)†	p-Value†	
Vericiguat - Placebo					1.2 (-0.5, 2.9)	0.180	

Note: Subjects who died during the study were assigned the worst possible score for all post-death visits up until the primary completion date (18Jun2019).
† Based on a longitudinal analysis of covariance model, with the change score as the dependent variable, including categorical terms for stratification factor, week, treatment group, and the week-by-treatment group interaction, with the baseline value as a continuous covariate, and including all post-randomization timepoints through Week 96.
For baseline and Week 32, N is the number of patients with non-missing assessments at the specific timepoint. For Change from Baseline, N is the number of patients with non-missing assessment in both baseline and Week 32.
CI = Confidence Interval, LS = Least Squares, SD = Standard Deviation.
Based on data up to the primary completion date (18Jun2019).

Source: CSR Table 11-16

Table 24 Analysis of Change from Baseline in EQ-5D-5L UK Index Score at Week 32, ITT Population, VICTORIA

	Baseline		Week 32		Change from Baseline at Week 32		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI†)
Vericiguat	2378	0.69 (0.24)	2021	0.58 (0.49)	1943	-0.12 (0.47)	-0.12 (-0.14, -0.10)
Placebo	2345	0.69 (0.23)	2009	0.55 (0.51)	1898	-0.15 (0.48)	-0.13 (-0.15, -0.11)
Treatment Comparison					Difference in LS Means (95% CI)†	p-Value†	
Vericiguat - Placebo					0.01 (-0.01, 0.04)	0.297	

Note: Subjects who died during the study were assigned the worst possible score for all post-death visits up until the primary completion date (18Jun2019).
† Based on a longitudinal analysis of covariance model, with the change score as the dependent variable, including categorical terms for stratification factor, week, treatment group, and the week-by-treatment group interaction, with the baseline value as a continuous covariate, and including all post-randomization timepoints through Week 96.
For baseline and Week 32, N is the number of patients with non-missing assessments at the specific timepoint. For Change from Baseline, N is the number of patients with non-missing assessment in both baseline and Week 32.
CI = Confidence Interval, LS = Least Squares, SD = Standard Deviation.
Based on data up to the primary completion date (18Jun2019).

Source: CSR Table 11-17

5.3.6.4. NT-proBNP

The geometric means of NT-proBNP decreased from Baseline to Week 32 in both treatment groups in all four quartiles. While the Geometric Mean Ratios (GMRs) between Week 32 and

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baseline decrease as the baseline NT-proBNP increases, the least square mean ratios of the GMRs between vericiguat and placebo were consistent among the four quartiles of baseline NT-proBNP values, as shown in Table 25.

Table 25 Analysis of Change from Baseline in NT-proBNP at Week 32, ITT Population, VICTORIA

Treatment	Baseline		Week 32		Geometric Mean Ratio (GMR): Week 32/Baseline	
	N	Geometric mean (SD)	N	Geometric mean (SD)	LS Mean (SE)†	95% CI
Overall population						
Vericiguat	2414	2928.4 (2.65)	1815	1729.2(3.39)	0.67 (1.02)	(0.65,0.69)
Placebo	2391	2886.8 (2.64)	1813	1875.1(3.42)	0.74 (1.02)	(0.72, 0.77)
LS Mean ratio‡					0.90 (0.86, 0.94)	p<0.0001
Q1 of baseline NT-proBNP						
Vericiguat	596	891.1 (1.79)	494	703.9 (2.83)	0.83 (1.03)	(0.78, 0.88)
Placebo	604	867.0 (1.71)	515	756.0 (2.80)	0.90 (1.03)	(0.85, 0.96)
LS Mean ratio					0.92 (0.85, 1.0)	p=0.045
Q2 of baseline NT-proBNP						
Vericiguat	613	2095.8 (1.18)	500	1459.7 (2.50)	0.68 (1.04)	(0.63, 0.73)
Placebo	589	2136.7 (1.19)	475	1635.0 (2.71)	0.76 (1.04)	(0.71, 0.81)
LS Mean ratio					0.90 (0.83, 0.97)	p=0.01
Q3 of baseline NT-proBNP						
Vericiguat	585	3873.8 (1.20)	442	2399.4 (2.54)	0.62 (1.04)	(0.58, 0.67)
Placebo	613	3823.8 (1.20)	463	2709.2 (2.59)	0.71 (1.04)	0(0.66, 0.76)
LS Mean ratio					0.87 (0.80, 0.95)	p=0.002
Q4 of baseline NT-proBNP						
Vericiguat	614	9946.7 (1.70)	379	4763.3 (3.21)	0.54 (1.05)	(0.50, 0.59)
Placebo	585	10066.8 (1.69)	360	5130.7 (3.16)	0.58 (1.05)	(0.53, 0.63)
LS Mean ratio					0.94 (0.84, 1.04)	p=0.24

Source: Reviewer's table, dataset: adlbit.

†Based on a longitudinal analysis of covariance model, with the change from baseline in log transformed value as the dependent variable, including categorical terms for stratification factor, week, treatment group, and the week-by-treatment group interaction, with the log transformed baseline value as a continuous covariate, and including all post-randomization timepoints through Week 32.

‡LS mean ratio between vericiguat and placebo of the geometric mean ratios (GMR) of Week 32 versus baseline.

For baseline and Week 32, N is the number of patients with non-missing assessments at the specific timepoint. For Change from Baseline, N is the number of patients with non-missing assessment in both baseline and Week 32.

CI = Confidence interval, LS = least squares, SD = standard deviation (back-transformed from SD of log of NT-proBNP value). SE = standard error (back-transformed from SD of log of NT-proBNP value).

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

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5.4. Review Issues Relevant to the Evaluation of Benefit

5.4.1. Proarrhythmic potential- Subgroup findings of CV mortality by baseline device use

Issue

Compared to placebo, vericiguat-treated subjects with an ICD or biventricular pacemaker at baseline tended to have lower CV mortality than those without a device in the VICTORIA trial. This finding in VICTORIA occurred in the context of numerically higher rates of CV death from the Phase 2 and Phase 3 trials of vericiguat in subjects with (b) (4). In particular, a higher incidence of sudden cardiac deaths was found in the vericiguat group than the placebo group in the HFpEF Phase 3 trial. (b) (4)

(b) (4)

Assessment

<u>VICTORIA Trial Data</u>

Differential treatment effects on CV mortality by device use at baseline (i.e., ICD or biventricular pacemaker) was observed in VICTORIA (Table 19). It is unclear how many of the biventricular pacing systems also had defibrillator capability (CRT-D). Specifically, the protective effect of vericiguat for CV mortality was considerable among subjects with the presence of one of these devices. In contrast, the HR was close to or greater than 1 among subjects without a device at baseline.

Regional Differences

Considering that there was regional variability in use of a cardiac device for HF treatment, the potential regional differences in this subgroup finding were evaluated (Table 25). Because the results were similar for ICD and biventricular pacemaker, device use at baseline (i.e., either an ICD or biventricular pacemaker) was used for this subgroup analysis.

Overall, the presence of a device at baseline was protective across all regions except for Asia-Pacific with respect to the HR for CV mortality. The HRs were close to or greater than 1 among subjects without a device at baseline; in particular, the HR was 1.6 for North America.

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Table 25 Subgroup Analysis of CV Mortality by Region and Device Use at Baseline, ITT Population, VICTORIA

			Vericiguat (N=2521)		Placebo (N=2519)		Vericiguat vs. Placebo	
Region	Baseline Device Use[1]	Median Baseline EF (%)	n/N	Event rate (% pt-yr)	n/N	Event rate (% pt-yr)	Hazard Ratio	95% CI
All regions	**Device**	**26**	**138 / 813**	**12.7**	**188 / 802**	**18.2**	**0.70**	**(0.56, 0.87)**
	No Device	**30**	**273 / 1708**	**12.9**	**252 / 1717**	**11.9**	**1.08**	**(0.91, 1.29)**
Western Europe	Device	28	38 / 234	11.6	44 / 213	15.6	0.75	(0.48, 1.15)
	No Device	32	33 / 209	11.4	33 / 230	10.3	1.10	(0.68, 1.79)
North America	Device	25	20 / 160	9.69	36 / 160	17.3	0.55	(0.32, 0.95)
	No Device	30	14 / 117	8.24	8 / 118	5.11	**1.59**	(0.66, 3.80)
Latin/South America	Device	25	9 / 60	13.1	14 / 51	24.6	0.55	(0.24, 1.27)
	No Device	28	46 / 302	13.7	47 / 311	13.5	1.01	(0.67, 1.51)
Eastern Europe	Device	25	50 / 243	14.5	77 / 264	22.8	0.64	(0.45, 0.92)
	No Device	30	114 / 605	15.0	108 / 581	14.7	1.02	(0.79, 1.33)
Asia-Pacific	Device	30	21 / 116	15.3	17 / 114	11.5	1.32	(0.70, 2.51)
	No Device	30	66 / 475	11.8	56 / 477	9.96	1.18	(0.83, 1.68)

[1]Subjects with an ICD or biventricular pacemaker implemented at baseline
Source: Reviewer's table, dataset: adsl, adtte, and adsoch, OCS Analysis Studio, Custom Table Tool

Reviewer's Comment: The protective effect of vericiguat with respect to CV mortality is considerably greater among subjects who had a device implemented at baseline. Subjects who had a device at baseline also had lower baseline LVEF compared to those without a device, indicating a "sicker" population. This finding is consistent across most regions except for Asia-Pacific. However, the mechanism behind these findings is not clear given the negative results from the TQT study and nonclinical safety pharmacology data (see sections below). Although the submitted data did not indicate proarrhythmic potential of vericiguat therapy, these studies had some methodological issues that limited the interpretation of the results. The comprehensive in vitro proarrhythmia assay (CiPA) was not conducted prior to the NDA submission.

Exploratory subgroup analysis based on baseline device use and indication

To further explore this review issue, subgroup analyses by baseline device use and whether or not subjects had Class I guideline-directed indications for a device for primary prevention of sudden death was conducted. In particular, among subjects who did not have a device at baseline, the comparison between those with and without an indication was of interest (Table 26). The categorization of whether a subject had an indication for an ICD or a biventricular pacemaker was based on the 2017 AHA/ACC/HRS guideline recommendations.[5]

Of note, subjects with an indication for a device at baseline who had the device demonstrated a significant reduction in CV death compared to those who did not have a device at baseline (either with or without an indication) (Table 26).

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Table 26 Subgroup Analysis by Device Use at Baseline and Indication, ITT Population, VICTORIA

Subgroup	Primary Endpoint			CV Death			HF Hospitalization		
	n/N	HR	*p*-value	n/N	HR	*p*-value	n/N	HR	*p*-value
+ Indication + Device	600/1365	0.79	0.004	286/1365	0.69	0.0018	491/1365	0.87	0.13
- Indication - Device	319/986	0.90	0.33	141/986	1.03	0.87	230/986	0.86	0.25
+ Indication - Device	850/2439	0.94	0.36	384/2439	1.10	0.33	628/2439	0.89	0.16

Source: Reviewer's Table datasets: adsl, adbase, adsoch, adeg and adttec

Multivariate model to assess risk factors for CV mortality

Subgroup analysis is subject to multiplicity effects and does not adjust for potential confounding factors. To assess the relationship between the subgroup factors of interest and CV mortality, a multivariate analysis was conducted (See Section 5.4.2). In brief, the differential effects on CV mortality by baseline device use were still observed and significant after adjusting for other factors in a multivariate model.

CV Deaths in Patients with HFpEF

Phase 3 study: VITALITY-HFpEF

This 6 month, double-blind, placebo-controlled study randomized 789 subjects (LVEF ≥ 45%) to evaluate the efficacy of vericiguat (10 mg and 15 mg) in improving physical functioning (KCCQ Physical limitation score) from Baseline to Week 24. (b) (4)

There was an imbalance in adjudicated deaths (CV and non-CV), with 7 deaths (6.4 per 100 patient-years; 4 CV deaths) in placebo, 15 deaths (14.1 per 100 patient-years; 12 CV deaths) in the 10 mg vericiguat group and 10 deaths (9.3 per 100 patient-years; 8 CV deaths) in the 15 mg group (Table 27). The incidences of death due to HF and sudden cardiac death were higher in the vericiguat treatment groups compared to placebo. There were no sudden cardiac deaths reported in the placebo group compared to 5 (1.9%, 4.7 per 100-patient year) in both of the vericiguat treatment groups.

Table 27 Reason for All Adjudicated Deaths, Full Analysis Set, VITALITY-HFpEF

Reason for Death	Placebo N=262 (100%)	Vericiguat 10mg N=263 (100%)	Vericiguat 15mg N=264 (100%)	Total N=789 (100%)
Total number of adjudicated deaths (%)	7 (2.7)	15 (5.7)	10 (3.8)	32 (4.1)
Cardiovascular Death	4 (1.5)	12 (4.6)	8 (3.0)	24 (3.0)
Heart failure	1 (0.4)	6 (2.3)	3 (1.1)	10 (1.3)
Other cardiovascular causes	1 (0.4)	0	0	1 (0.1)
Stroke	2 (0.8)	1 (0.4)	0	3 (0.4)
Sudden cardiac death	0	5 (1.9)	5 (1.9)	10 (1.3)
Non-Cardiovascular Death	2 (0.8)	3 (1.1)	2 (0.8)	7 (0.9)
Undetermined Death	1 (0.4)	0	0	1 (0.1)

Source: The applicant's CSR Table 9-35

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Phase 2 Study: SOCRATES-PRESERVED

This randomized, parallel-group, placebo-controlled, double-blind, multi-center dose finding Phase 2 study explored the pharmacodynamic effects, safety and tolerability, and pharmacokinetics of 4 vericiguat dose regimens (1.25 mg, 2.5 mg, 2.5 to 5 mg, and 2.5 to 10 mg) over 12 weeks in patients with worsening HF and HFpEF. The study was not powered to evaluate clinical outcomes. Nevertheless, CV deaths at Week 12 were observed in 4 subjects (4.2%) in the 2.5 to 5 mg vericiguat group, 1 subject (1%) in the 2.5 to 10 mg vericiguat group and 0 in other groups (i.e., placebo, 1.25 mg, and 2.5 mg vericiguat groups).

In addition, SAEs with a fatal outcome were reported in 11 of 475 subjects (2.3%); 6 events were treatment-emergent, of which 1 SAE of cardiogenic shock was considered by the investigator to be related to the study drug (in 2.5-5-mg group, last dose was 2.5 mg). The incidence was lowest in the placebo and 2.5-mg vericiguat treatment group (1 subject; 1.1% in each group) compared with 2 subjects (2.1%) in the 2.5-10-mg group and 7 subjects (7.4%) in the 2.5-5-mg group, no deaths were reported in the 1.25-mg dose group. There was one on-treatment sudden death in the 2.5-5 mg group.

QT Evaluation

Clinical

The Interdisciplinary Review Team for cardiac safety studies (IRT) reviewed the TQT study and the ECG data in the VICTORIA trial (link, DARRTS on 8/25/2020). The IRT concluded that no large mean increases in the QTc interval (i.e., > 20 msec) were detected with vericiguat 10 mg at steady-state in the TQT study. However, small increases in the QTc interval (i.e., 10 msec) could not be excluded because of limitations in the study design (i.e., ΔΔQTcF could not be derived because there was no concurrent placebo administration). The IRT also conducted categorical analyses for different ECG measurements in both the TQT study and VICTORIA. None of the subjects was in the outlier category for QTc, PR or QRS in the TQT study. Categorical analysis results for the VICTORIA trial do not show any significant percent increase in the vericiguat group compared to the placebo group, overall or in the subgroups with or without a device implanted at baseline (i.e., ICD or biventricular pacemaker at baseline).

Nonclinical Safety Pharmacology Assessment

The IRT commented on the applicant's nonclinical safety pharmacology assessment which included an evaluation of the effects of vericiguat on the hERG potassium channel and an in vivo QT study in dogs. The IRT concluded that vericiguat does not seem to interact substantially with hERG channels at the therapeutic exposure level and does not have significant effects on QRS and QTc intervals in dogs. However, the nonclinical evaluation did not follow best practices; thus, the results of these studies cannot be included in an integrated risk assessment as described in the new ICH S7B Q&As.

Reviewer's Comment:

Per the discussions in the Mid-Cycle Communication meeting, the applicant agreed to conduct comprehensive cardiac channel testing under worse case scenarios (e.g., higher holding potentials and faster stimulation rates for the peak sodium current) to better understand the potential clinical effects of vericiguat. The IRT reviewed the applicant's proposed protocol for

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the nonclinical cardiac ion channel studies and provided recommendation for the hERG, peak sodium, and Kv7.1/mink (IKs) experiments, including changes to ensure that the experiments reflect "worst case scenarios."

5.4.2. NT-proBNP Subgroup findings

Issue

Unfavorable efficacy results in subjects in the highest baseline NT-proBNP quartile were observed in the VICTORIA trial.

Assessment

Efficacy outcomes by NT-proBNP at baseline

Unfavorable efficacy results in subjects in the highest baseline NT-proBNP quartile were observed for both components of the primary efficacy endpoint (Figure 7).

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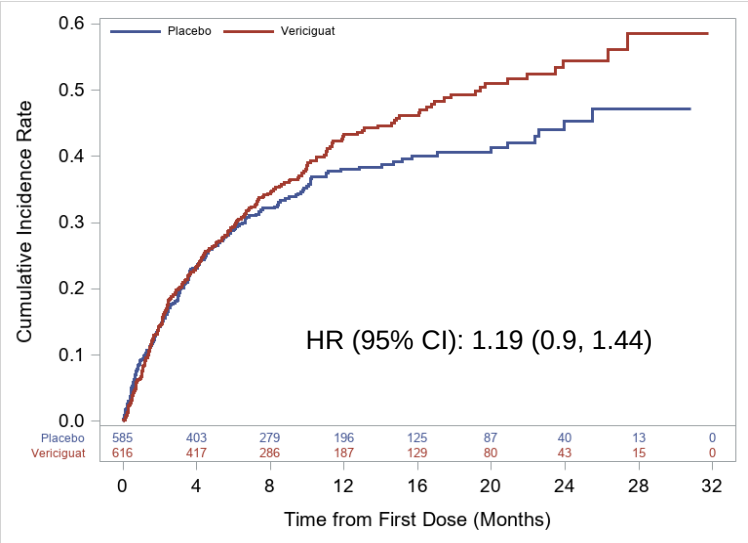
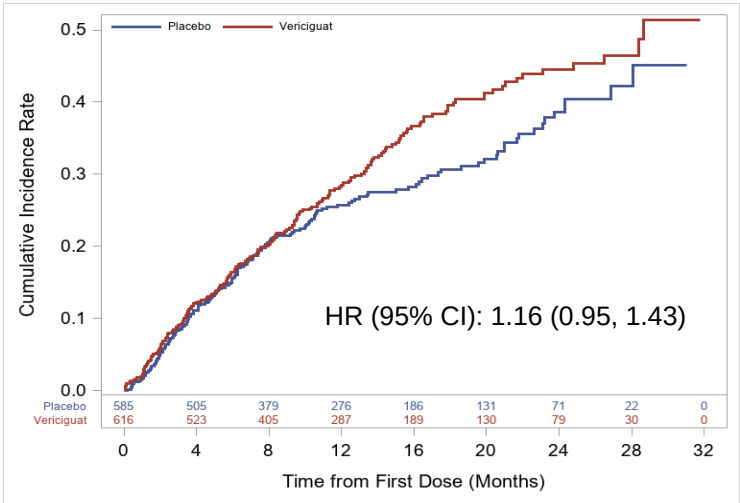
Figure 7 Kaplan-Meier Plot for (a) First HF Hospitalization and (b) CV Death Among Subjects in The Fourth Quartile of Baseline NT-proBNP (> 5314 pg/mL)

(a)



(b)



Source: Reviewer's figure, dataset: adsl, adbase and adttec

Exploratory analyses evaluating the upper segments of NT-proBNP (i.e., 1/8 and 1/10) demonstrate that the inferior efficacy results were consistent in subjects with higher baseline NT-proBNP, particularly for CV mortality. Figure 8 below depicts the Kaplan-Meier plot for the time to CV Death for the two treatment groups among the subjects in the highest decile of baseline NT-proBNP.

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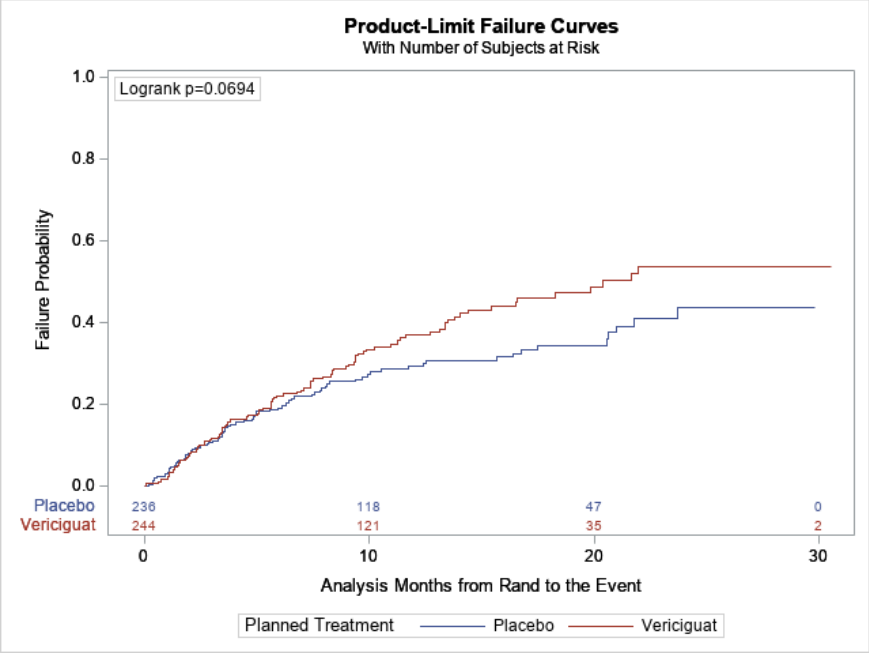
Figure 8 Kaplan-Meier Plot for The Time to CV Death Among Subjects in the Highest Decile of Baseline NT-proBNP (> 10273 pg/mL)



A higher incidence of CV death in the vericiguat group than placebo was only observed in the highest baseline NT-proBNP quartile and the difference was primarily driven by a higher incidence of sudden cardiac death (Table 28). Similar results were found for the on-treatment CV deaths (Appendix III.12.3). Sudden cardiac death was the most frequently reported cause of on-treatment CV death in the vericiguat-treated subjects in the highest NT-proBNP quartile (7.1% vs. 3.9% in the vericiguat and placebo groups, respectively, Appendix III.12.3).

Table 28 Causes of Cardiovascular Death by Baseline NT-proBNP Quartile, ITT Population, VICTORIA

	Vericiguat				Placebo			
	Q1 (<=1556) (N=599)	Q2 (1557 - 2816) (N=613)	Q3 (2817 - 5314) (N=586)	Q4 (>5314) (N=616)	Q1 (<=1556) (N=604)	Q2 (1557 - 2816) (N=589)	Q3 (2817 - 5314) (N=613)	Q4 (>5314) (N=585)
CV death[1]	34 (5.7)	64 (10.4)	92 (15.7)	208 (33.8)	47 (7.8)	78 (13.2)	115 (18.8)	169 (28.9)
Heart Failure	8 (1.3)	30 (4.9)	38 (6.5)	82 (13.3)	26 (4.3)	29 (4.9)	52 (8.5)	72 (12.3)
Sudden Cardiac Death	9 (1.5)	11 (1.8)	28 (4.8)	56 (9.1)	9 (1.5)	29 (4.9)	30 (4.9)	39 (6.7)
Undetermined Cause Of Death	16 (2.7)	17 (2.8)	22 (3.8)	51 (8.3)	9 (1.5)	15 (2.5)	22 (3.6)	47 (8.0)
Other Cardiovascular Event	0	4 (0.7)	2 (0.3)	7 (1.1)	1 (0.2)	3 (0.5)	1 (0.2)	3 (0.5)
Stroke	0	0	0	7 (1.1)	2 (0.3)	2 (0.3)	4 (0.7)	4 (0.7)
Myocardial Infarction	1 (0.2)	2 (0.3)	2 (0.3)	5 (0.8)	0	0	6 (1.0)	4 (0.7)

[1] All CV deaths up to the primary completion data (18 Jun 2019)
Source: Reviewer's Table datasets: adsl, adbase, and adeff, OCS Analysis Studio, Custom Table Tool

Reviewer's Comment: This finding raises concern in the context of the excess sudden cardiac death that has been identified in the phase 3 HFpEF trial (see Section 5.4.1 and Table 27). A higher incidence of on-treatment sudden cardiac death was also observed in the vericiguat-

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treated subjects in the highest NT-proBNP quartile (>5314 pg/mL) and supports the possibility that this finding could be drug-related.

Given the concern about the potential proarrhythmic effects of vericiguat (Section 5.4.1), the assessment of CV mortality by device use in the highest baseline NT-proBNP quartile was conducted. Table 29 shows that a higher incidence of on-treatment CV death including sudden cardiac death in the vericiguat group was primarily observed among subjects who did not have an ICD at baseline. Vericiguat-treated subjects in the highest quartile of baseline NT-proBNP with an ICD at baseline had lower CV mortality compared to placebo-treated subjects. Similar results were found based on biventricular pacemaker use at baseline (Table 30)

Reviewer's comment: It is important to understand that many CRT devices (biventricular pacing systems) also have defibrillation capabilities, so are in fact CRT-D devices. The number of CRT devices in VICTORIA that also had defibrillation capability (i.e., were CRT-D devices) was not reported separately.

Table 29 Causes of On-Treatment Cardiovascular Death by Use of an ICD at Baseline among Subjects in The Highest NT-proBNP Quartile, ITT Population, VICTORIA

	Vericiguat Q4 (>5314) (N=616)		Placebo Q4 (>5314) (N=585)	
	No ICD (N=450)	**ICD (N=166)**	**No ICD (N=427)**	**ICD (N=158)**
CV death (on treatment)[1]	**96 (21.3)**	**17 (10.2)**	**62 (14.5)**	**23 (14.6)**
Sudden cardiac death	40 (8.9)	4 (2.4)	21 (4.9)	2 (1.3)
Heart failure	32 (7.1)	7 (4.2)	18 (4.2)	16 (10.1)
Undetermined cause of death	16 (3.6)	3 (1.8)	19 (4.4)	4 (2.5)
Other cardiovascular event	4 (0.9)	1 (0.6)	1 (0.2)	0
Myocardial infarction	2 (0.4)	1 (0.6)	2 (0.5)	1 (0.6)
Stroke	2 (0.4)	1 (0.6)	1 (0.2)	0

[1] CV death occurred within 14 days after the last dose of study drug

Source: Reviewer's Table, datasets: adsl, adbase, adsoch and adeff, OCS Analysis Studio, Custom Table Tool

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Table 30 Causes of On-Treatment Cardiovascular Death by Use of a Biventricular Pacemaker at Baseline among Subjects in The Highest NT-proBNP Quartile, ITT Population, VICTORIA

	Vericiguat Q4 (>5314) (N=616)		Placebo Q4 (>5314) (N=585)	
	No Biventricular Pacemaker (N=522)	Biventricular Pacemaker (N=94)	No Biventricular Pacemaker (N=493)	Biventricular Pacemaker (N=92)
CV death (on treatment) [1]	**105 (20.1)**	**8 (8.5)**	**69 (14.0)**	**16 (17.4)**
Sudden cardiac death	41 (7.9)	3 (3.2)	21 (4.3)	2 (2.2)
Heart failure	35 (6.7)	4 (4.3)	25 (5.1)	9 (9.8)
Undetermined cause of death	19 (3.6)	0	18 (3.7)	5 (5.4)
Other cardiovascular event	4 (0.8)	1 (1.1)	1 (0.2)	0
Myocardial infarction	3 (0.6)	0	3 (0.6)	0
Stroke	3 (0.6)	0	1 (0.2)	0

[1]CV death occurred within 14 days after the last dose of study drug
Source: Reviewer's Table, datasets: adsl, adbase, adsoch and adeff, OCS Analysis Studio, Custom Table Tool

Reviewer's Comment: These subgroup findings for CV mortality prompted additional evaluation on the excess mortality noted in subjects with the highest baseline NT-proBNP quartile, utilizing a multivariate model (see multivariate analysis below).

Baseline Characteristics across NT-proBNP subgroups

We further evaluated differences in baseline characteristics and concomitant medications between upper and lower baseline NT-proBNP quartiles to help determine who might have a negative treatment effect of vericiguat. Table 31 shows that patients in the upper quartile of the baseline NT-proBNP were more advanced in age (18% are at least 81 year old compared to 12% among those in lower quartiles of baseline NT-proBNP); they had higher BMIs and lower LVEFs (33% are in the first quartile of BMI compared to 23% among those in lower quartiles of baseline NT-proBNP; 59% have an LVEF below 30% compared to 46% among those in lower quantiles of baseline NT-proBNP); they were more likely to be in higher heart failure categories (52% are in NYHA Class III compared to 36% among those in lower quartiles of baseline NT-proBNP); and they also tended to have lower eGFRs (20% are below 30 in eGFR compared to 7% among those in lower quartiles of baseline NT-proBNP). In addition, they were less likely to use triple therapy for HF (51% compared to 63% among those in lower quartiles of baseline NT-proBNP).

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Table 31 Differences of Subject Baseline Characteristics and Device Usage between The Highest Quartile of NT-proBNP and The Rest, ITT Population, VICTORIA

	Q1 to Q3 (<=5314) (N=3604)	Q4 (>5314) (N=1201)
Age (>= 81 yeas)	418 (11.6)	221 (18.4)
Region (North America)	422 (11.7)	227 (8.7)
NYHA class		
Class II	2285 (63.4)	549 (45.7)
Class III	1283 (35.6)	622 (51.8)
BMI		
Q1	823 (22.9)	388 (32.5)
Q4	994 (27.7)	195 (16.3)
LVEF		
<30%	1667 (46.3)	702 (58.7)
>= 30 to 40%	1374 (38.2)	370 (30.9)
>= 40 to 45%	556 (15.5)	125 (10.4)
eGFR		
<= 30	237 (6.6)	241 (20.2)
> 30 to <= 60	1439 (40.3)	588 (49.2)
> 60	1897 (53.1)	367 (30.7)
Biventricular Pacemaker Usage	508 (14.1)	186 (15.5)
ICD Usage	1000 (27.8)	324 (27.0)
Triple Therapy	2265 (62.9)	609 (50.7)

Source: Reviewer's Table datasets: adsl, adbase, adsoch and adeff

Multivariate Analysis

CV mortality

To better understand the relationship between NT-proBNP and CV mortality, a multivariate Cox-proportional model, stratified by region, was conducted to assess time to CV mortality as a continuous function of baseline NT-proBNP, other important risk factors (e.g. device use at baseline), and the interaction terms of interest (i.e., treatment by NT-proBNP and treatment by device use). Because the distribution of baseline NT-proBNP was right skewed, we transformed NT-proBNP on a logarithmic scale (base 2). After adjusting for important covariates, the two interaction terms remained significant (i.e., treatment by NT-proBNP, $p = 0.03$ and treatment by device, $p < 0.0001$). See Appendix III.12.4.1 for the outputs of the model.

Figure 9 depicts how the treatment effect of vericiguat on CV mortality changes with baseline NT-proBNP level among subjects with and without a device at baseline. As shown in the figures, the HR of CV mortality increases as baseline NT-proBNP increases; however, treatment effect of vericiguat also depended on device use at baseline. Among subjects who did not have a device at baseline (~ 65% of ITT population, Figure 9a), the HR of vericiguat was > 1 where the baseline NT-proBNP level was > 3000 pg/mL, whereas the treatment effect (HR < 1) was maintained across entire levels of baseline NT-proBNP among subjects with a device at baseline (Figure 9b). Table 32 shows how the treatment effect changes as the baseline NT-proBNP increases in both groups of baseline device usage.

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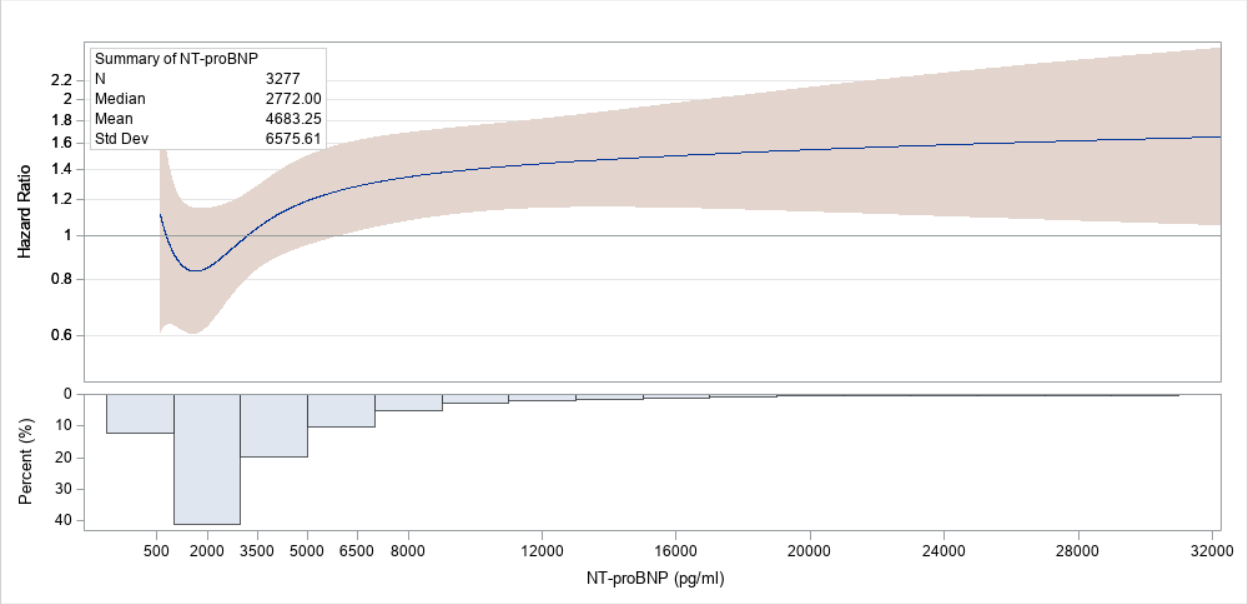
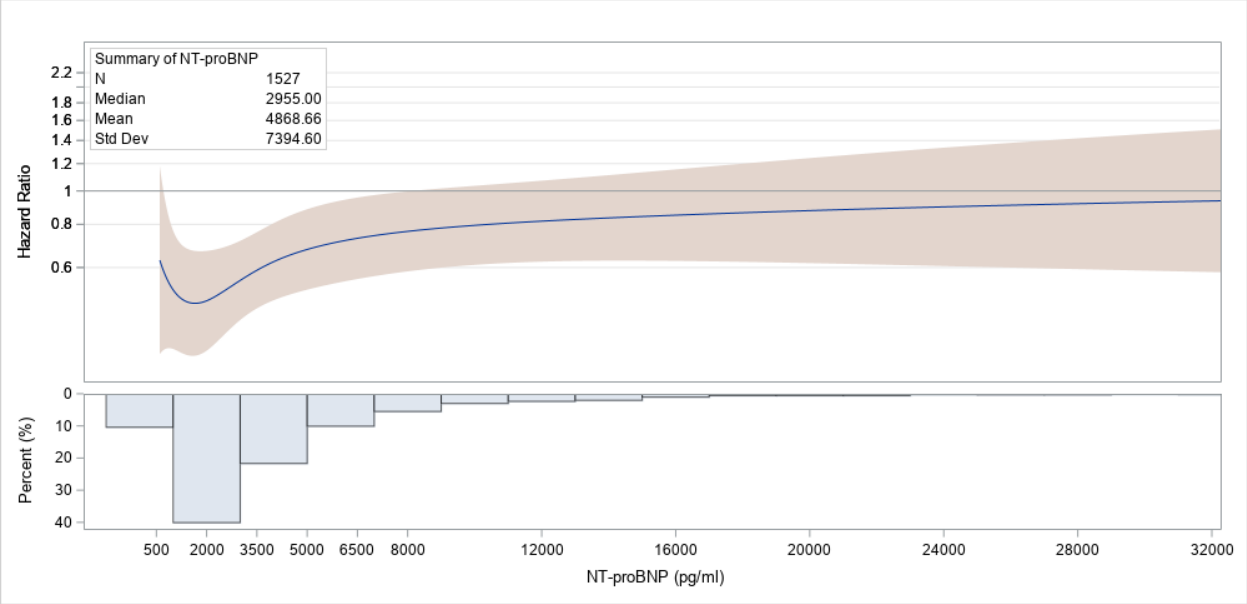
Figure 9 Hazard Ratio of CV Mortality by Baseline NT-proBNP among Subjects (a) Without A Device and (b) With A Device at Baseline

(a)



(b)



Hazard ratios for vericiguat vs. placebo across NT-proBNP level are calculated from Cox proportional hazards model stratified by region with factors for continuous NT-proBNP at randomization, treatment, the interaction between treatment group and NT-proBNP, device use at baseline (i.e., ICD or biventricular pacemaker), the interaction term between treatment and device use, age, LVEF, NYHA Class and Triple therapy. NT-proBNP was transformed on a logarithmic scale (base 2) and using a restricted cubic spline with four knots at 5th, 35th, 65th and 95th. Band on the plot shows 95% confidence interval calculated using the same model. The bottom part of the figure represents the distribution of NT-proBNP at randomization for a given subset in VICTORIA.

Source: Reviewer's analysis, datasets: adsl, adbase, adsoch and adttec.

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Table 32 Estimated Hazard Ratio of CV Mortality by Baseline NTproBNP by Device Use at Baseline, ITT Population, VICTORIA

Baseline NT-proBNP level	Device		No Device	
	Hazard Ratio[a]	95% CI[a]	Hazard Ratio[a]	95% CI[a]
1000	0.52	(0.35, 0.77)	0.91	(0.63, 1.32)
2000	0.48	(0.35, 0.77)	0.85	(0.63, 1.15)
3000	0.55	(0.42, 0.72)	0.97	(0.78, 1.22)
4000	0.62	(0.48, 0.81)	1.10	(0.89, 1.37)
5000	0.68	(0.52, 0.89)	1.20	(0.95, 1.50)
6000	0.71	(0.54, 0.94)	1.26	(1.00, 1.59)
7000	0.74	(0.57, 0.97)	1.31	(1.04, 1.65)
8000	0.76	(0.59, 1.00)	1.35	(1.08, 1.69)
9000	0.78	(0.60, 1.02)	1.38	(1.11, 1.72)
10000	0.80	(0.61, 1.04)	1.41	(1.13, 1.75)

[a] Hazard ratio and 95% CI calculated from a multivariate Cox-proportional model (see Appendix III.12.4.1)
Source: Reviewer's analysis, datasets: adsl, adbase, adsoch and adttec.

First HF Hospitalization

A similar multivariate analysis was conducted for first HF hospitalization. After adjusting for important covariates, the treatment by NT-proBNP interaction term remained significant (i.e., treatment by NT-proBNP, $p < 0.01$). Unlike the model for CV mortality, the treatment effect for HF hospitalization did not depend on device use at baseline. See Appendix III.12.4.2 for the outputs of the model. Figure 10 shows how the treatment effect of vericiguat on first HF hospitalization changes with baseline NT-proBNP level. Whereas the HR increases as baseline NT-proBNP increases, the relationship was shallower then that for CV mortality. The HR was > 1 at NT-proBNP > 5000 pg/mL and plateaued at around 1.1 (See Appendix III.12.4.2., Table 49)

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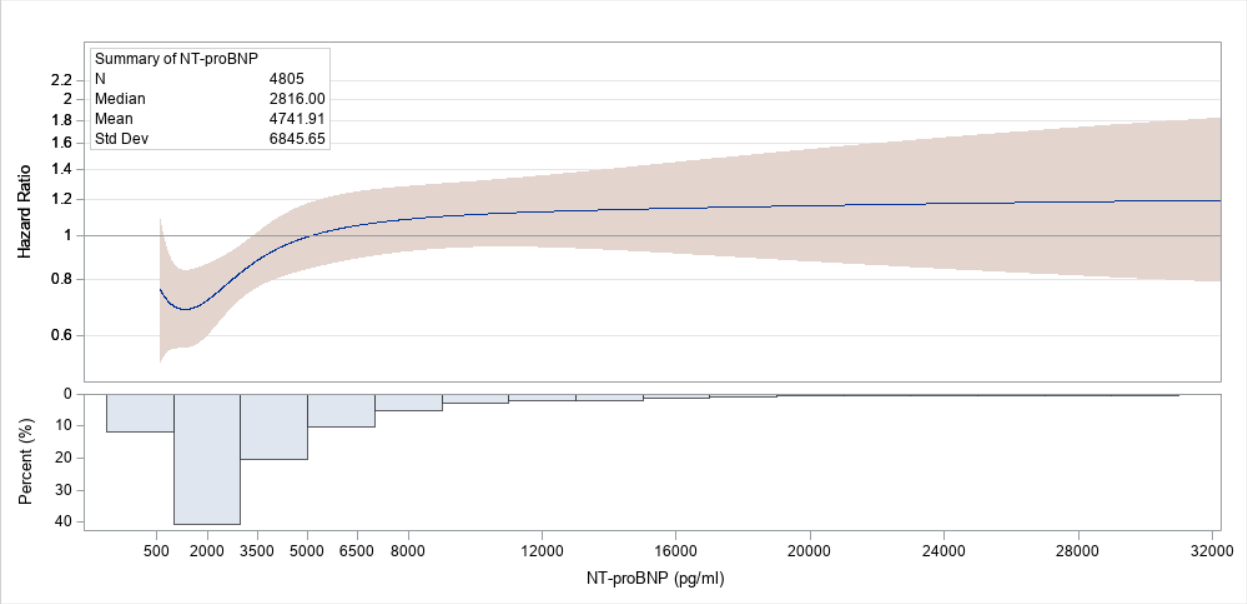
Figure 10 Hazard Ratio of First HF Hospitalization by Baseline NT-proBNP, ITT Population, VICTORIA



Hazard ratios for vericiguat vs. placebo across NT-proBNP level are calculated from Cox proportional hazards model stratified by region with factors for continuous NT-proBNP at randomization, treatment, the interaction between treatment group and NT-proBNP, device use at baseline (i.e., ICD or biventricular pacemaker), sex, BMI, eGFR, LVEF, NYHA Class and Triple therapy. NT-proBNP was transformed on a logarithmic scale (base 2) and using a restricted cubic spline with four knots at 5th, 35th,65 and 95th. Band on the plot shows 95% confidence interval calculated using the same model. The bottom part of the figure represents the distribution of NT-proBNP at randomization in VICTORIA.

Source: Reviewer's analysis, datasets: adsl, adbase, adsoch and adttec.

Primary Efficacy Endpoint

A similar multivariate analysis was conducted for the primary efficacy endpoint. After adjusting for important covariates, the treatment by NT-proBNP interaction term remained significant (i.e., treatment by NT-proBNP, $p = 0.002$), but the treatment by baseline device use was marginally significant ($p = 0.06$). See Appendix III.12.4.3 for the outputs of the model. Figure 10 shows how the treatment effect of vericiguat of the primary efficacy endpoint changed with baseline NT-proBNP level among subjects with or without a device at baseline. The HR increases as baseline NT-proBNP increases; however, treatment effect depended on device use at baseline. Among subjects who did not have a device at baseline (~ 65% of ITT population), the HR was > 1 if their baseline NT-proBNP level was close to or greater than 5000 pg/mL, and plateaued at around 1.2.

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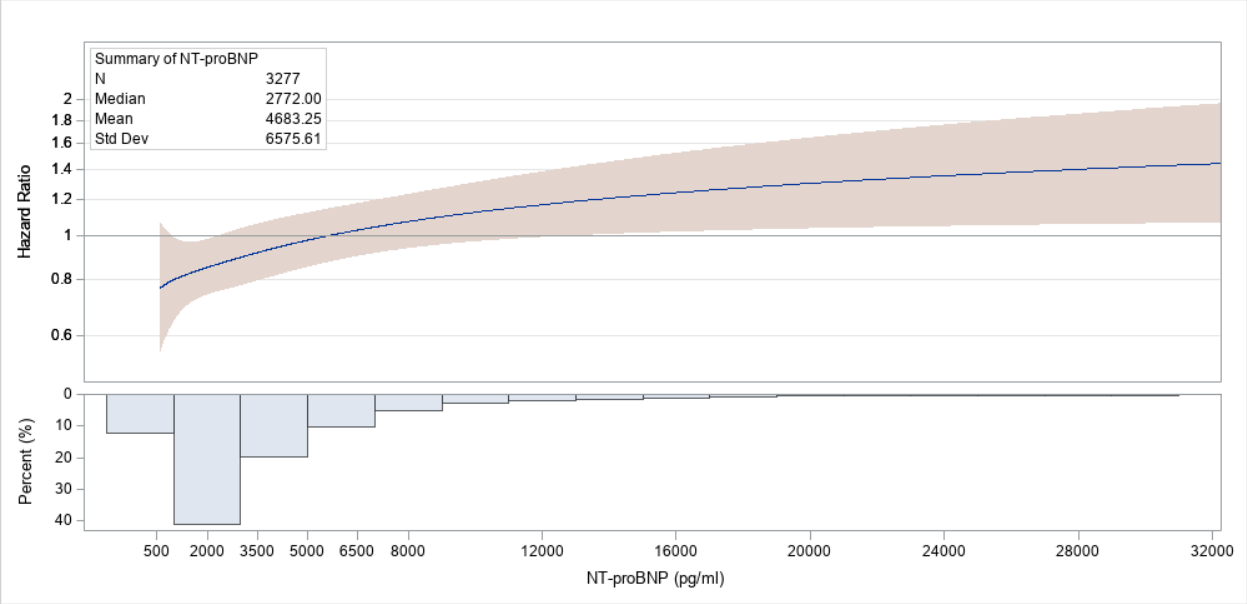
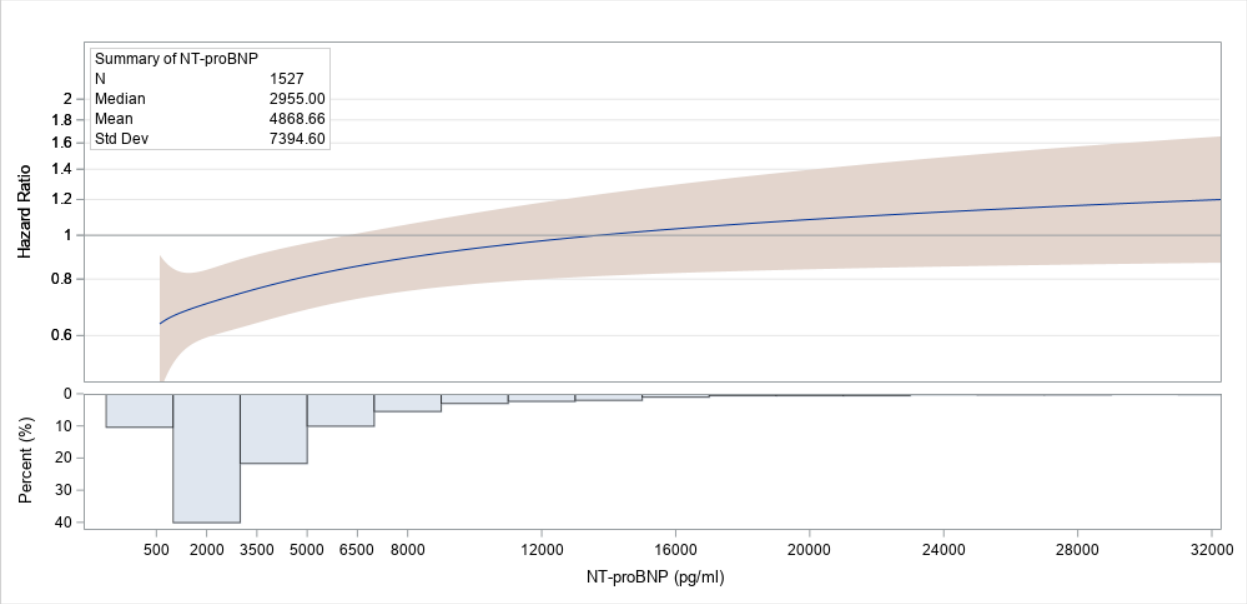
Figure 11 Hazard Ratio of the Primary Efficacy Endpoint by Baseline NT-proBNP among Subjects (a) Without A Device and (b) With A Device at Baseline

(a)



(b)



Hazard ratios for vericiguat vs. placebo across NT-proBNP level are calculated from Cox proportional hazards model stratified by region with factors for continuous NT-proBNP at randomization, treatment, the interaction between treatment group and NT-proBNP, device use at baseline (i.e., ICD or biventricular pacemaker), the interaction term between treatment group and device use at baseline, sex, BMI, eGFR, LVEF, NYHA Class and Triple therapy. NT-proBNP was transformed on a logarithmic scale (base 2) and using a restricted cubic spline with four knots at 5th, 35th, 65th and 95th. Band on the plot shows 95% confidence interval calculated using the same model. The bottom part of the figure represents the distribution of NT-proBNP at randomization in VICTORIA.

Source: Reviewer's analysis, datasets: adsl, adbase, adsoch and adttec.

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Non-Clinical Cardiac Ion Channels Studies

Following a teleconference with FDA on Oct 7, 2020, the applicant agreed to perform additional ion channel studies incorporating the CiPA protocol to assess the effects of vericiguat and its M1 metabolite on hERG, KvLQT/mink (IKs), and Nav1.5 currents. The applicant submitted the results of these studies on November 18, 2020. Overall, these channel studies also showed no evidence of membrane channel interactions with vericiguat exposure that would result in proarrhythmia.

Conclusion

There is no evidence from non-clinical data including CiPA cardiac ion channel studies and the TQT study to support a possible mechanism (i.e., proarrhythmic potential) for the clinical efficacy findings regarding the cardiac device use at baseline in VICTORIA (5.4.1). (b) (4) However, given the CV death findings observed in the HFpEF trials and the unfavorable CV mortality trend observed in the prospectively defined upper quartile analysis of baseline NT-proBNP from VICTORIA, the clinical review team recommends that these findings be disclosed in the Warnings and Precautions section in labeling.

6. Risk and Risk Management

6.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The potential safety concerns based on the nonclinical data are embryo-fetal toxicity and effects on bone metabolism. In animal reproduction studies, oral administration of vericiguat to pregnant rabbits during organogenesis, at ≥ 4 times the human exposure with the maximum recommended human dose (MRHD) of 10 mg, resulted in malformations of the heart and major vessels, as well as increased numbers of abortions and resorptions. Vericiguat is present in the mammary glands of lactating rats and it is likely that vericiguat or its metabolites are present in human milk. In a pre-postnatal development study, vericiguat administered orally to rats from gestation until lactation showed maternal toxicity (decreases in food consumption and body weight gain), which resulted in decreased pup body weight gain (with doses ≥ 10 times the MRHD) and pup mortality (with doses 24 times the MRHD) during the preweaning period.

For bone metabolism, preclinical evidence suggests a concentration-dependent effect of cGMP on long bone growth and remodeling, most relevant to bone growth in children and adolescents. Effects were noted in a juvenile rat pilot study when the pups were administered an amount of vericiguat exceeding a maximally tolerated dose. The bone effects were most apparent in the shorter-term studies using adolescent rats and included hypertrophy of the growth plate, hyperostosis, and remodeling of metaphyseal and diaphyseal bone. The bone effects were not obvious in the 2-year carcinogenicity studies in rats and mice and were not reported for the

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repeat dose toxicology studies in dogs or the 6-month toxicity study in rats. In the 13-week repeat dose toxicity study in rats, bone hyperostosis and remodeling were observed at 30 mg/kg.

6.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

The potential safety concerns were reviewed based on known information for the approved member of the pharmacologic class, riociguat. The Warnings and Precautions for riociguat include embryo-fetal toxicity, hypotension, bleeding, and pulmonary edema in patients with pulmonary veno-occlusive disease. An additional adverse drug reaction (ADR) of interest for riociguat included anemia. Adverse events of special interest (AESI) for vericiguat in VICTORIA included AEs suggestive of symptomatic hypotension, syncope, and hepatic injury.

6.3. Potential Safety Concerns Identified Through Postmarket Experience

Vericiguat is not approved or marketed in the United States or worldwide.

6.4. FDA Approach to the Safety Review

Safety analyses were conducted for the treated population (patients who received at least one dose of study drug) for VICTORIA and includes adverse events (AEs) that were collected up to 14 days after discontinuation of study drug. The analysis included a review of data quality, adverse events, laboratory data, baseline characteristics, concomitant medications, and vital sign datasets. Adverse events were analyzed by MedDRA [version 22.0] preferred term and by pooling similar adverse events (referred to as the MedDRA SMQ or FMQ). The review team did not identify any major data quality or integrity issues that precluded performing a safety review. No major issues were identified with respect to recording, coding, and categorizing AEs. The applicant’s translations of verbatim terms to MedDRA preferred terms for the events reported in VICTORIA were reviewed and found to be acceptable.

6.5. Adequacy of the Clinical Safety Database

Total patient exposures were consistent with ICH guidelines and sufficient to assess the safety of vericiguat for the proposed indication, dosage regimen, duration, and patient population. In VICTORIA, 2,519 subjects received at least one dose of vericiguat, and the mean duration of exposure was 375.5 days. A summary of exposure for VICTORIA is shown in Table 33.

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Table 33 Duration of Exposure, Safety Population, VICTORIA

Parameter	Vericiguat N=2519 2.5 mg	5 mg	10 mg	Placebo N=2515
Any duration (at least 1 dose)	2517 (99.9)	2285 (90.7)	2063 (81.9)	2515 (100.0)
Duration of treatment (days)				
Mean (SD)	35.0 (70.1)	48.2 (90.1)	362.0 (239.2)	374.7 (250.9)
Median (min, max)	15.0 (1, 918)	14.0 (1, 861)	310.0 (1, 935)	342 (1, 966)
Patients treated, by duration, n (%)				
<1 month[1]	2092 (83.1)	1687 (67.0)	92 (3.7)	140 (5.6)
≥1 month	425 (16.9)	598 (23.7)	1971 (78.2)	2375(94.4)
≥3 months	239 (9.5)	326 (12.9)	1861 (73.9)	2222 (88.3)
≥6 months	94 (3.7)	147 (5.8)	1523 (60.5)	2021 (80.3)
≥12 months[1]	24 (1)	49 (1.9)	885 (35.1)	1172 (46.6)

Reviewer's Analysis: datasets adsl.xpt, exsum.xpt; Software: JMP
Abbreviations: N, number of subjects in group; n, number of subjects with given treatment duration; SD, standard deviation.
[1] 1 month = 30 days; 12 months = 365 days

6.6. Safety Findings and Safety Concerns Based on Review of the Clinical Safety Database

6.6.1. Overall Adverse Event Summary

The AEs, SAEs, and SAEs with fatal outcome were similar across treatment groups, with placebo-treated patients having a higher proportion. Adverse events leading to dose modification, interruption, or reduction occurred in a marginally higher proportion of the vericiguat-treated patients. Table 34 provides an overview of the AEs in the VICTORIA safety population.

Table 34 Overview of Adverse Events,[1] Controlled Trial Safety Population, VICTORIA

Event	Vericiguat N=2519 n (%)	Placebo N=2515 n (%)	Relative Risk (95% CI)
Any AE	2027 (80.5)	2036 (81.0)	0.99 (0.97, 1.02)
Moderate or severe AEs (Grade 3-5)[2]	1386 (55.0)	1421 (56.5)	0.97 (0.93, 1.02)
SAE	826 (32.8)	876 (34.8)	0.94 (0.87, 1.02)
SAEs with fatal outcome	83 (3.3)	85 (3.4)	0.97 (0.72, 1.31)
AE leading to discontinuation of study drug	177 (7.0)	160 (6.4)	1.10 (0.90, 1.36)
AE leading to dose modification of study drug	653 (25.9)	606 (24.1)	1.07 (0.98, 1.18)
AE leading to interruption of study drug	484 (19.2)	460 (18.3)	1.05 (0.94, 1.18)
AE leading to reduction of study drug	72 (2.9)	62 (2.5)	1.16 (0.83, 1.62)

Reviewer's analysis; adsl.xpt, adae.xpt; OCS Analysis Studio
[1] Includes treatment-emergent AE defined as any adverse event that occurred after the first dose of drug up to 14 days after discontinuation of study drug.
[2] Moderate: events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities; Severe: events interrupt the patient's usual daily activity, are incapacitating with inability to do usual activities, or significantly affect clinical status and warrant intervention and/or close follow-up.
Abbreviations: AE, adverse event; SAE, serious adverse event; CI, confidence interval; N, number of subjects in group; n, number of subjects with at least one event.

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6.6.2. Deaths

Deaths, including CV and non-CV death, were considered events meeting efficacy endpoint criteria and were initially adjudicated by an independent CEC. If an event submitted for adjudication was determined by the CEC not to meet endpoint criteria, the event was then considered for AE reporting. Therefore, the number of AEs resulting in a fatal outcome differs from the number of CEC adjudicated deaths in the efficacy analyses. Table 35 provides an overview of the deaths in VICTORIA.

There were 570 treatment-emergent CEC adjudicated deaths (CV and non-CV). The incidence of treatment-emergent deaths and AEs with fatal outcomes was lower in the vericiguat treatment group. The proportions of subjects with non-CV death were similar between treatment groups. Although the total CV deaths were lower for vericiguat-treated patients, sub-group analyses revealed an imbalance in SCD, driven by patients with a baseline NT-proBNP level > 5314 pg/mL. Additional analyses are presented in Section 5.4.1.

Table 35 Deaths in The Safety Population, VICTORIA

Deaths	Vericiguat N=2519 n (%)	Placebo N=2515 n (%)
Total AE with fatal outcome	83 (3.3)	85 (3.4)
Treatment-emergent deaths[1]	280 (11.1)	290 (11.5)
CV Event	186 (7.4)	199 (7.9)
Heart failure	77 (3.1)	94 (3.7)
Myocardial infarction	8 (0.3)	8 (0.3)
Other CV Event	10 (0.4)	7 (0.3)
Stroke	3 (0.1)	8 (0.3)
Sudden cardiac death	88 (3.5)	82 (3.3)
Non-CV Event	50 (2.0)	40 (1.6)
Undetermined cause of death[2]	44 (1.7)	51 (2.0)
Non-treatment emergent deaths	269 (10.7)	270 (10.7)
CV Event	140 (5.6)	157 (6.2)
Heart failure	105 (4.2)	106 (4.2)
Myocardial infarction	3 (0.1)	3 (0.1)
Other CV Event	3 (0.1)	3 (0.1)
Stroke	5 (0.2)	8 (0.3)
Sudden cardiac death	24 (1.0)	37 (1.5)
Non-CV Event	55 (2.2)	58 (2.3)
Undetermined cause of death	74 (2.9)	55 (2.2)

Source: Reviewer's analysis [adsl.xpt and adeff.xpt dataset(s) and OCS Analysis Studio; JMP]
[1] Treatment-emergent defined as any death that occurred after the first dose of drug up to 14 days after discontinuation.
Abbreviations: N, number of subjects in group; n, number of deaths.

6.6.3. Serious Adverse Events

Overall, SAEs were reported more frequently in placebo-treated patients in VICTORIA. The imbalances in specific preferred terms or groupings of preferred terms between vericiguat- and placebo-treated patients included anemia, liver injury, and syncope (Table 36). Additional analyses for these are presented in Section 6.6.6.

Reference ID: 4733225

Table 36 Serious Adverse Events by Descending Difference (>0.2%) Order, Safety Population, VICTORIA

Serious Adverse Event[1,2]	Vericiguat (N = 2519) n (%)	Placebo (N = 2515) n (%)	Risk Difference (95% CI)
Patients with at least one SAE	826 (32.8)	876 (34.8)	-2.0 (-0.6, 4.6)
Syncope[3]	52 (2.1)	36 (1.4)	0.7 (0.0, 1.4)
Anaemia[4]	40 (1.6)	22 (0.9)	0.7 (0.1, 1.3)
Liver Injury[5]	25 (1.0)	12 (0.5)	0.5 (0.0, 1.0)
Chronic kidney disease	38 (1.5)	31 (1.2)	0.3 (-0.4, 0.9)
Cellulitis	25 (1)	18 (0.7)	0.3 (-0.2, 0.8)
Acute kidney injury[6]	92 (3.7)	87 (3.5)	0.2 (-0.8, 1.3)
Chronic obstructive pulmonary disease	36 (1.4)	30 (1.2)	0.2 (-0.4, 0.9)
Gastroenteritis	16 (0.6)	10 (0.4)	0.2 (-0.2, 0.6)
Lung infection	9 (0.4)	3 (0.1)	0.2 (0.0, 0.5)
Urosepsis	6 (0.2)	0 (0.0)	0.2 (0.1, 0.4)
Gastrointestinal hemorrhage	12 (0.5)	7 (0.3)	0.2 (-0.1, 0.5)
Ascites	8 (0.3)	3 (0.1)	0.2 (-0.1, 0.5)
Coronary artery disease	7 (0.3)	2 (0.1)	0.2 (0.0, 0.4)
General physical health deterioration	6 (0.2)	1 (0.0)	0.2 (0.0, 0.4)
Orthostatic hypotension	6 (0.2)	1 (0.0)	0.2 (0.0, 0.4)
Subdural hematoma	6 (0.2)	1 (0.0)	0.2 (0.0, 0.4)
Dyspnea	11 (0.4)	7 (0.3)	0.2 (-0.2, 0.5)
Cardiogenic shock	8 (0.3)	4 (0.2)	0.2 (-0.1, 0.4)
Pneumonia aspiration	6 (0.2)	2 (0.1)	0.2 (-0.1, 0.4)
Musculoskeletal pain	4 (0.2)	0 (0.0)	0.2 (0.0, 0.3)

Source: Reviewer's analysis [adsl and adae; Software: MAED]
[1] Coded as MedDRA preferred terms
[2] Terms included are those that occurred more often in the treatment than comparator group
[3] Includes preferred terms dizziness, presyncope, dizziness postural, loss of consciousness
[4] Includes preferred terms blood loss anemia, autoimmune hemolytic anemia, normochromic normocytic anaemia
[5] Includes preferred terms hepatic congestion, hepatocellular injury, liver disorder, hepatic enzyme abnormal, hepatic failure, hepatitis acute, hepatic enzyme increased, hepatitis toxic, acute hepatic failure, liver function test increased, liver function test abnormal, ischemic hepatitis
[6] Includes preferred terms renal impairment and renal failure
Abbreviations: CI, confidence interval; N, number of subjects in group; n, number of subjects with adverse event

6.6.4. Dropouts and/or Discontinuations Due to Adverse Events

The proportions of subjects who discontinued treatment due to an AE were similar in both treatment groups. The most frequently reported AEs for discontinuation were AEs related to hypotension and anemia. Table 37 provides an overview of the AEs leading to discontinuation. Although treatment discontinuation rates due to AEs were low overall, the rate was slightly higher for vericiguat until approximately 22 months (day 700) after start of treatment (Figure 12).

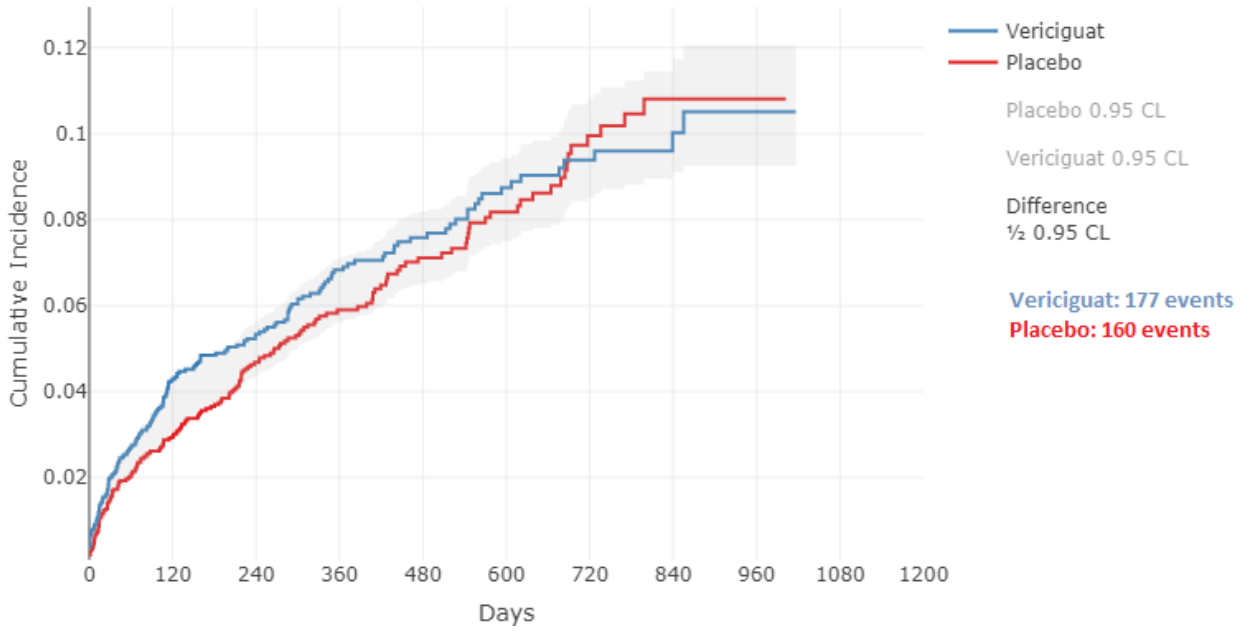
Reference ID: 4733225

Table 37 Adverse Events Leading to Discontinuation by Descending Difference (>0.2%) Order, Safety Population, VICTORIA

Adverse Event[1,2]	Vericiguat N=2519 n (%)	Placebo N=2515 n (%)	Risk Difference (95% CI)
Patients with at least 1 AE leading to discontinuation	177 (7.0)	160 (6.4)	0.6 (-0.8, 2.0)
Anaemia[3]	22 (0.9)	12 (0.5)	0.4 (-0.1, 0.9)
Chronic obstructive pulmonary disease	9 (0.4)	2 (0.1)	0.3 (0.0, 0.6)
Hypotension[4]	62 (2.5)	59 (2.3)	0.2 (-0.7, 1.1)
Dyspnea	15 (0.6)	9 (0.4)	0.2 (-0.2, 0.6)
Atrial Fibrillation	10 (0.4)	6 (0.2)	0.2 (-0.1, 0.6)
Asthenia	9 (0.4)	4 (0.2)	0.2 (-0.1, 0.6)
Nausea	6 (0.2)	1 (0.0)	0.2 (0.0, 0.5)
Gastroesophageal reflux disease	5 (0.2)	1 (0.0)	0.2 (0.0, 0.5)

Source: Reviewer's analysis [adsl.xpt, adae.xpt and MAED]
[1] Coded as MedDRA preferred terms
[2] Terms included are those that occurred more often in the treatment than comparator group
[3] FMQ Anaemia Broad
[4] FMQ Hypotension Broad
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in group; n, number of subjects with adverse event; PT, preferred term.

Figure 12 Kaplan-Meier Plot of Patients with Permanent Discontinuation of Study Drug due to an Adverse Event, Safety Population, VICTORIA



Source: Reviewer's analysis [adsl xpt, adae.xpt and OCS The Adverse Event Temporal Visualization Tool]

6.6.5. Treatment-Emergent Adverse Events

The most common AEs occurring more frequently in the vericiguat group than in the placebo group were anemia, GI events (nausea, dyspepsia), headache, hypotension, and syncope. Most

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of these events are related to the pharmacological mode of action (relaxation of smooth muscles leading to hemodynamic changes, headache, and GI side effects). Tables 38 and 39 provide the AEs occurring at 0.5% higher frequency in the vericiguat-treated patients than in placebo. Additional analyses for anemia, hypotension, and syncope are presented in Section 6.6.6. A number of the adverse event groupings in Tables 38 and 39 are FDA MedDRA queries (FMQs).

Table 38. Adverse Events1 Occurring at 0.5% Higher Frequency in Vericiguat Than Placebo Group, Safety Population, VICTORIA

Preferred Term[2]	Vericiguat N=2519 n (%)	Placebo N=2515 n (%)	Risk Difference (95% CI)
Anaemia[3]	243 (9.6)	185 (7.4)	2.2 (0.7, 3.7)
Dyspepsia	67 (2.7)	27 (1.1)	1.6 (0.8, 2.3)
Syncope[4]	273 (10.8)	237 (9.4)	1.4 (-0.3, 3.1)
Nausea	96 (3.8)	67 (2.7)	1.2 (0.2, 2.1)
Gastroesophageal reflux disease	44 (1.8)	17 (0.7)	1.1 (0.5, 1.7)
Hypotension[5]	432 (17.1)	410 (16.3)	0.8 (-1.3, 2.9)
Dizziness	169 (6.7)	150 (6)	0.7 (-0.6, 2.1)
Chronic obstructive pulmonary disease	76 (3)	58 (2.3)	0.7 (-0.2, 1.6)
Influenza	74 (2.9)	57 (2.3)	0.7 (-0.2, 1.6)
Accidental overdose[6]	62 (2.5)	46 (1.8)	0.6 (-0.2, 1.4)

Source: Reviewer's analysis [adsl.xpt, adae.xpt and MAED]
[1] Treatment-emergent adverse event defined as occurring after the first dose of drug up to 14 days after discontinuation
[2] Coded as MedDRA preferred terms
[3] FMQ Anaemia Broad
[4] Includes preferred terms dizziness, presyncope, dizziness postural, loss of consciousness
[5] FMQ Hypotension Broad
[6] Defined as any dose higher than the maximal target dose prescribed
Abbreviations: CI, confidence interval; N, number of subjects; n, number of subjects with adverse event; PT, preferred term.

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Table 39 FDA MedDRA Queries[1] Occurring at 0.5% Higher Frequency in Vericiguat Than Placebo, Safety Population, VICTORIA

FMQ Broad	Vericiguat N=2519 n (%)	Placebo N=2515 n (%)	Risk Difference (95% CI)
Dyspepsia	286 (11.4)	223 (8.9)	2.5 (0.8, 4.2)
Anaemia	243 (9.6)	185 (7.4)	2.2 (0.7, 3.7)
Syncope	590 (23.4)	539 (21.4)	2 (-0.3, 4.3)
Nausea	133 (5.3)	94 (3.7)	1.6 (0.5, 2.8)
Vomiting	137 (5.4)	100 (4)	1.4 (0.2, 2.6)
Headache	91 (3.6)	63 (2.5)	1.1 (0.1, 2.1)
Dizziness	228 (9.1)	203 (8.1)	1 (-0.6, 2.6)
Hypotension	432 (17.1)	410 (16.3)	0.8 (-1.3, 2.9)
Vertigo	212 (8.4)	191 (7.6)	0.8 (-0.7, 2.3)
Abdominal pain	91 (3.6)	75 (3)	0.6 (-0.4, 1.6)
Bronchospasm	179 (7.1)	167 (6.6)	0.5 (-0.9, 1.9)
FMQ Narrow			
Anaemia	241 (9.6)	184 (7.3)	2.3 (0.7, 3.8)
Dyspepsia	106 (4.2)	54 (2.1)	2.1 (1.1, 3.0)
Hypotension	412 (16.4)	377 (15)	1.4 (-0.6, 3.4)
Nausea	96 (3.8)	67 (2.7)	1.1 (0.2, 2.1)
Headache	90 (3.6)	63 (2.5)	1.1 (0.1, 2.0)
Dizziness	228 (9.1)	203 (8.1)	1 (-0.6, 2.5)
Abdominal pain	89 (3.5)	74 (2.9)	0.6 (-0.4, 1.6)
Syncope	101 (4)	88 (3.5)	0.5 (-0.5, 1.6)

Source: Reviewer's analysis [adsl.xpt, adae.xpt and JMP]
[1] Treatment-emergent adverse event defined as occurring after the first dose of drug up to 14 days after discontinuation
Abbreviations: CI, confidence interval; N, number of subjects; n, number of subjects with adverse event; PT, preferred term.

6.6.6. Adverse Events of Special Interest

The pre-defined AESIs for VICTORIA included symptomatic hypotension, syncope, and predefined alterations in liver function tests (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥ 3 X ULN and bilirubin [BILI] ≥ 2 X ULN and alkaline phosphatase [ALP] < 2 X ULN). Overall, the incidence of these events was higher in the vericiguat group. Table 40 provides a summary of the pre-defined AESIs in VICTORIA. AESIs based on the pharmacologic class includes anemia and bleeding risk. Safety analyses for all AESIs are presented below.

Reference ID: 4733225

Table 40 Pre-defined Adverse Events[1] of Special Interest, Safety Population, VICTORIA

	Vericiguat N=2519 n (%)	Placebo N=2515 n (%)	Risk Difference (95% CI)
Experienced any AESI	332 (13.1)	278 (11.1)	2.0 (0.2, 3.8)
Symptomatic hypotension[2]	229 (9.1)	198 (7.9)	1.2 (-0.3, 2.7)
Syncope[3]	101 (4.0)	87 (3.5)	0.5 (-0.6, 1.6)
Predefined alterations in LFTs[4]	23 (0.9)	13 (0.5)	0.4 (-0.1, 0.9)

Source: Reviewer's analysis [adsl.xpt, adae.xpt and Analysis Studio]
[1] Treatment-emergent adverse event defined as occurring after the first dose of drug up to 14 days after discontinuation
[2] Included the following PTs: circulatory collapse, dizziness, dizziness postural, hypotension, orthostatic hypotension, presyncope, procedural hypotension
[3] Included the following PTs: syncope, pre-syncope, loss of consciousness, and circulatory collapse.
[4] AST or ALT ≥3 × ULN and BILI ≥2 × ULN and ALP <2 × ULN
Abbreviations: CI, confidence interval; N, number of subjects; n, number of subjects with adverse event; PT, preferred term.

6.6.6.1. Symptomatic Hypotension

The incidence of AEs classified as symptomatic hypotension (a decrease in blood pressure [BP] that may provoke near syncope, dizziness or similar symptoms) was 9.1% in the vericiguat group, corresponding to an event rate of 8.9 per 100 patient years, and 7.9% in the placebo group, corresponding to an event rate of 7.7 per 100 patient years (Table 41). However, the incidence of SAEs related to hypotension was greater in placebo-treated patients. The timing of symptomatic hypotension events was similar between the vericiguat and placebo groups (Figure 13). The BP mean changes from baseline among treatment groups were also similar. For SBP, the mean change from Baseline at Week 32 in the vericiguat group was an increase of 0.64 mmHg versus decrease of 0.5 mmHg in the placebo group; diastolic BP (DBP) decreased approximately 1 mm Hg in the vericiguat group and 0.23 mmHg in the placebo group. Subgroup analyses among baseline characteristics, dose, and concomitant medications did not reveal a significant imbalance, with females and patients under 65 years old having the greatest risk difference (Figure 14). In the majority of cases, the events were manageable, did not require specific therapy, and did not result in an increase in study treatment discontinuation.

Reference ID: 4733225

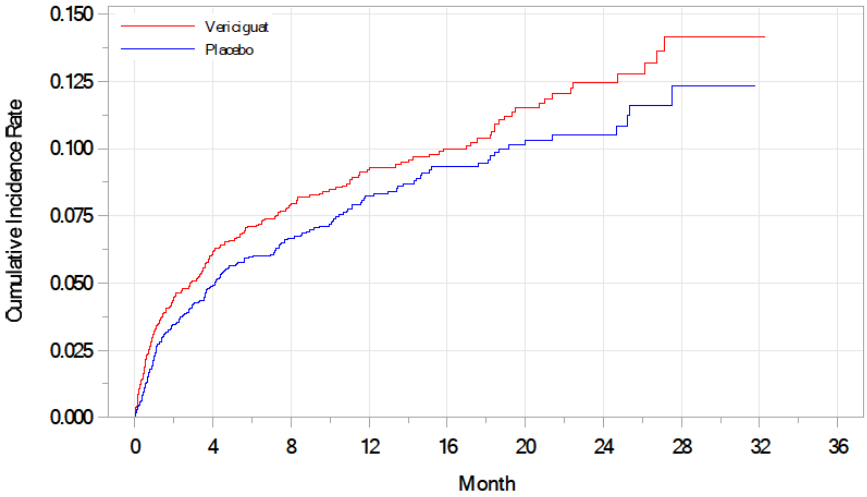
Table 41 Incidence of AESI Symptomatic Hypotension, Safety Population, VICTORIA

	Vericiguat (N=2519)	Placebo (N=2515)	Risk Difference (95% CI)
Symptomatic Hypotension, AE	229 (9.1)	198 (7.9)	1.2 (-0.3, 2.7)
Preferred Term, AE[1]			
Circulatory collapse	1 (0.03)	0 (0.0)	0.03 (-0.1, 0.2)
Dizziness	0 (0.0)	1 (0.04)	-0.04 (-0.1, 0.2)
Dizziness postural	1 (0.03)	0 (0.0)	0.03 (-0.1, 0.2)
Hypotension	212 (8.4)	182 (7.2)	1.2 (-0.3, 2.7)
Orthostatic hypotension	24 (1.0)	20 (0.8)	0.2 (-0.3, 0.7)
Presyncope	3 (0.1)	1 (0.0)	0.1 (-0.1, 0.3)
Procedural hypotension	0 (0.0)	1 (0.04)	-0.04 (-0.1, 0.2)
Symptomatic Hypotension, SAE	30 (1.2)	37 (1.5)	-0.3 (-0.3, 1.0)
Preferred Term, SAE			
Dizziness	0 (0.0)	1 (0.0)	0 (-0.1, 0.2)
Hypotension	26 (1.0)	36 (1.4)	-0.4 (-0.2, 1.0)
Orthostatic hypotension	5 (0.2)	1 (0.0)	0.2 (0, 0.5)
Presyncope	1 (0.0)	0 (0.0)	0 (-0.1, 0.2)

Reviewer's Table Source: adsl.xpt and adae.xpt; OCS Analysis Studio, Custom Table Tool

[1] Patient may have reported more than one AE

Figure 13 Kaplan-Meier Plot for Cumulative Event Rate of Symptomatic Hypotension, Safety Population, VICTORIA



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

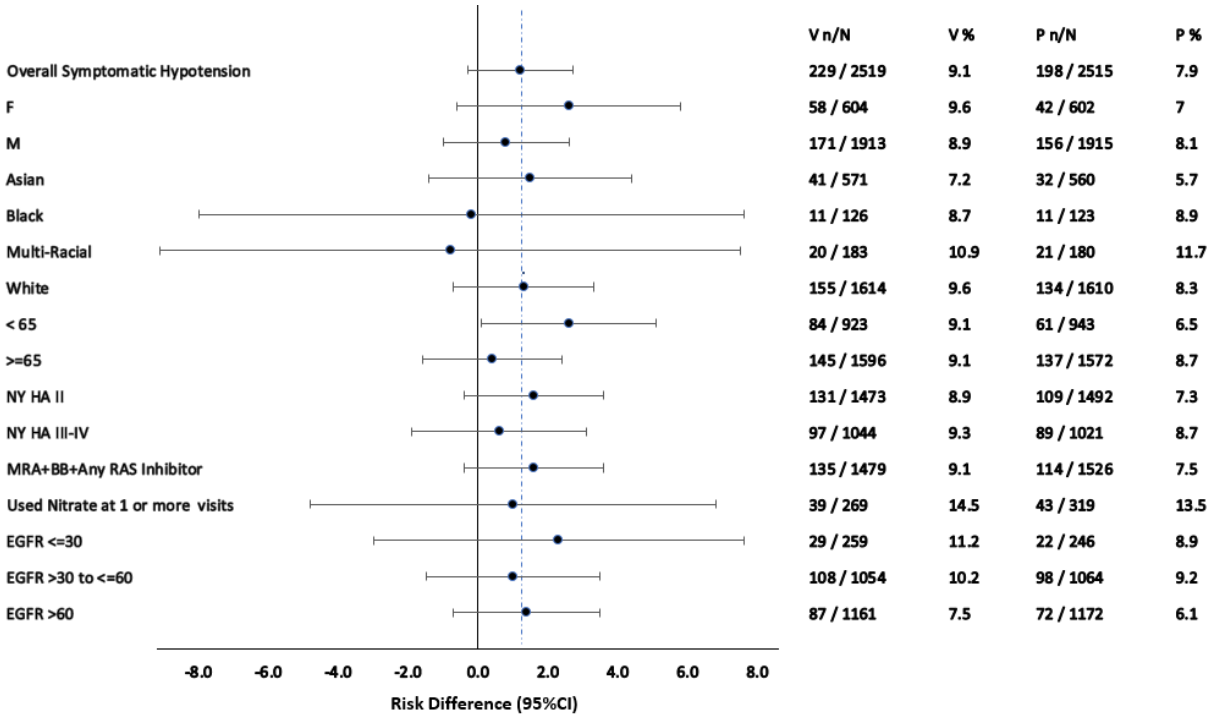
Cumulative number of events

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

Source: applicant Figure 2.7.4-hfref: 1; Summary of Clinical Safety

Reference ID: 4733225

Figure 14 Symptomatic Hypotension by Subgroup, Safety Population, VICTORIA



Reviewer's Figure Source: adae xpt, adsl xpt, adbase xpt and JMP

6.6.6.2. Syncope

The incidence of syncope AEs was low and similar between treatment groups, corresponding to 3.9 and 3.4 per 100 patient-years for vericiguat and placebo, respectively (Table 42). The time to onset was similar in both treatment groups (Figure 15). Fall or fracture AEs occurring within 2 days of a syncopal event were very low and balanced between treatment groups, vericiguat (n = 12 [0.5%]) and placebo (n = 14 [0.6%]). A subgroup analysis among baseline characteristics, dose, or concomitant medications revealed syncopal events occurred more frequently in the CCSA angina Class I/II. No association was observed between concomitant short-acting nitrate use (Figure 16). In the majority of cases, the events did not result in study treatment discontinuation.

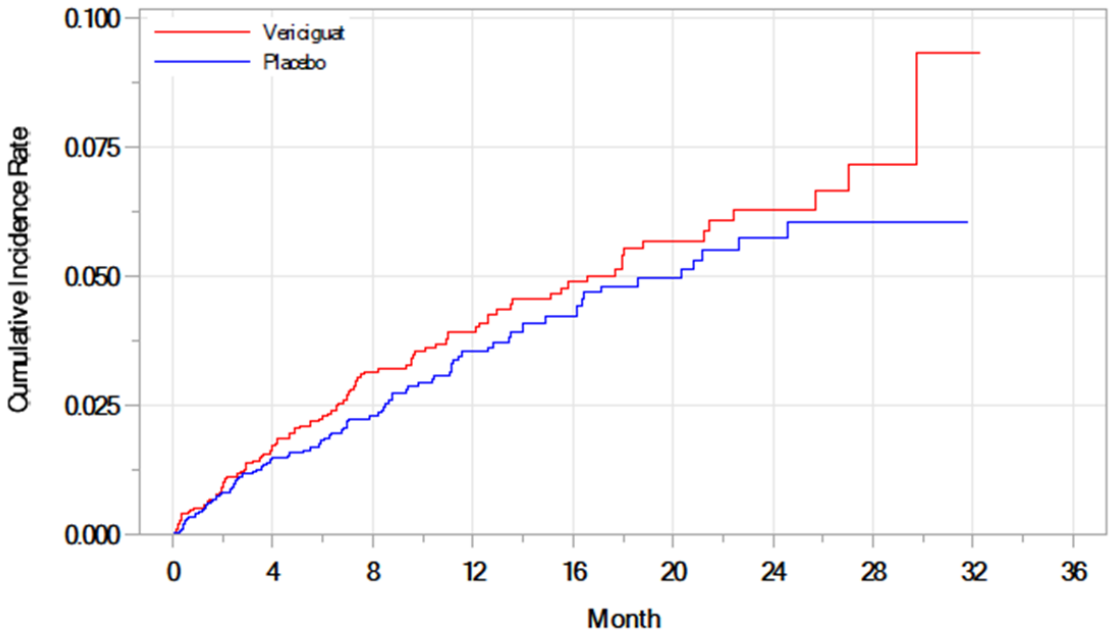
Reference ID: 4733225

Table 42 Incidence of AESI Syncope, Safety Population, VICTORIA

	Vericiguat (N=2519)	Placebo (N=2515)	Risk Difference (95% CI)
Syncope, AE	101 (4.0)	87 (3.5)	0.5 (-0.6, 1.6)
Preferred Term			
Loss of consciousness	0 (0.0)	1 (0.03)	-0.03 (-0.1, 0.2)
Syncope	101 (4.0)	86 (3.4)	0.6 (-0.4, 1.7)
Syncope, SAE	43 (1.7)	33 (1.3)	0.4 (-0.3, 1.1)
Loss of consciousness	0 (0.0)	1 (0.03)	-0.03 (-0.1, 0.2)
Syncope	43 (1.7)	32 (1.3)	0.4 (-0.3, 1.1)

Reviewer's Table Source: adsl.xpt and adae.xpt; OCS Analysis Studio, Custom Table Tool

Figure 15 Kaplan-Meier Plot for Cumulative Event Rate of Syncope, Safety Population, VICTORIA



Subjects at Risk

Vericiguat	2519	2112	1630	1143	820	576	343	131	1	0
Placebo	2515	2144	1652	1150	820	571	328	108	0	0

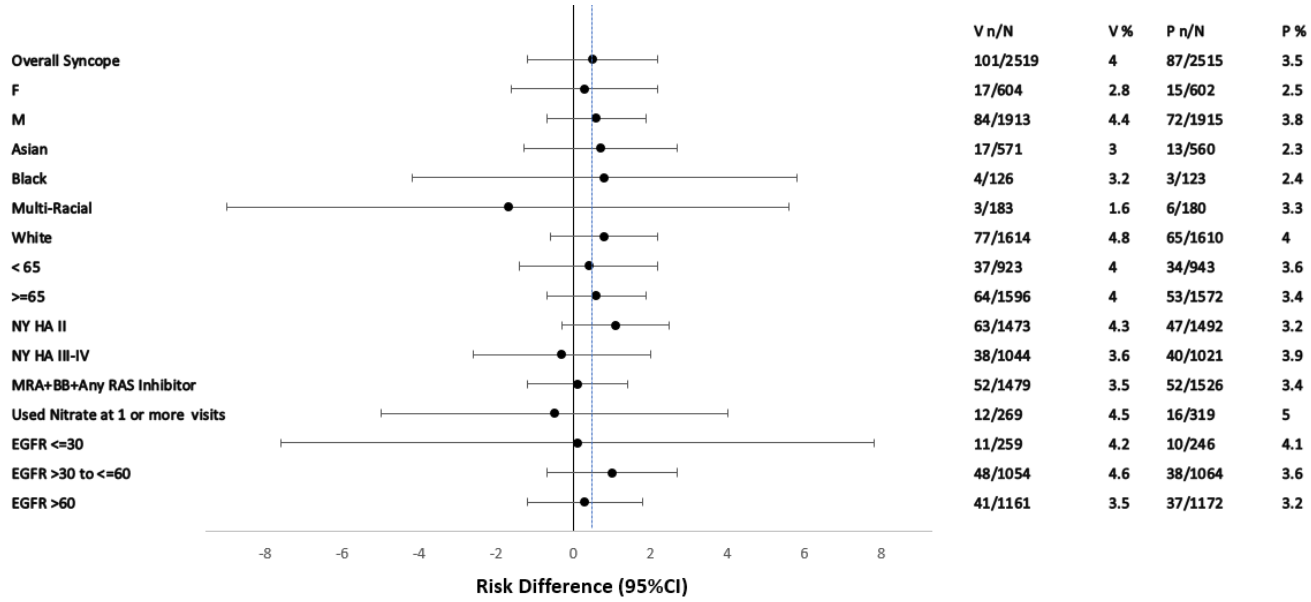
Cumulative number of events

Vericiguat	0	40	68	79	89	95	98	100	101	101
Placebo	0	35	51	69	76	82	86	87	87	87

Source: applicant Figure 2.7.4-hfref: 3; Summary of Clinical Safety

Reference ID: 4733225

Figure 16 Syncope by Subgroup, Safety Population, VICTORIA



Reviewer's Figure Source: adae xpt, adsl xpt, adbase xpt, adniuac xpt, and JMP

6.6.6.3. Hepatic Injury

The proportions of subjects with hepatic AEs or who met protocol-specified laboratory criteria (AST or ALT ≥ 3 × ULN and bilirubin ≥ 2 × ULN and ALP < 2 × ULN) were low, but slightly higher in the vericiguat group compared with the placebo group (Table 43). After review of the individual cases, none were determined to be associated with vericiguat; there was no evidence of an exposure-response relationship. All cases on vericiguat had an alternative explanation (most commonly HF decompensation) or did not recur with rechallenge. The majority of patients continued vericiguat with no alterations in dose.

Table 43 Incidence of AESI Hepatic Injury, Safety Population, VICTORIA

	Vericiguat (N=2519)	Placebo (N=2515)	Risk Difference (95% CI)
Met (AST or ALT ≥ 3 × ULN and bilirubin ≥ 2 × ULN and ALP < 2 × ULN)[1]	7 (0.3)	5 (0.2)	0.1 (-0.2, 0.4)
Hepatic Events, AE[2]	23 (0.9)	13 (0.5)	0.4 (-0.1, 0.9)
Acute hepatic failure	0 (0.0)	3 (0.1)	-0.1 (-0.1, 0.3)
Alanine aminotransferase increased	2 (0.1)	1 (0.04)	0.1 (-0.1, 0.3)
Aspartate aminotransferase increased	1 (0.04)	1 (0.04)	0.0 (-0.1, 0.2)
Blood alkaline phosphatase increased	1 (0.04)	0 (0.0)	0.01 (-0.1, 0.2)
Blood bilirubin increased	2 (0.1)	1 (0.04)	0.1 (-0.1, 0.3)
Hepatic congestion	2 (0.1)	0 (0.0)	0.1 (-0.1, 0.3)
Hepatic enzyme abnormal	1 (0.04)	0 (0.0)	0.01 (-0.1, 0.2)
Hepatic enzyme increased	6 (0.2)	3 (0.1)	0.1 (-0.1, 0.4)
Hepatic function abnormal	1 (0.04)	3 (0.1)	-0.1 (-0.1, 0.3)
Hepatitis acute	1 (0.04)	0 (0.0)	0.01 (-0.1, 0.2)
Hepatitis toxic	0 (0.0)	1 (0.04)	-0.04 (-0.1, 0.2)
Ischemic hepatitis	3 (0.1)	1 (0.04)	0.1 (-0.1, 0.3)

Reference ID: 4733225

	Vericiguat (N=2519)	Placebo (N=2515)	Risk Difference (95% CI)
Liver function test abnormal	2 (0.1)	0 (0.0)	0.1 (-0.1, 0.3)
Liver function test increased	1 (0.04)	1 (0.04)	0.0 (-0.1, 0.2)
Liver injury	3 (0.1)	0 (0.0)	0.1 (-0.1, 0.3)
Multiple organ dysfunction syndrome	1 (0.04)	0 (0.0)	0.01 (-0.1, 0.2)
Hepatic Event, SAE[2]	15 (0.6)	7 (0.3)	0.3 (-0.1, 0.7)
Acute hepatic failure	0 (0.0)	3 (0.1)	-0.1 (-0.1, 0.3)
Alanine aminotransferase increased	0 (0.0)	1 (0.04)	-0.04 (-0.1, 0.2)
Aspartate aminotransferase increased	0 (0.0)	1 (0.04)	-0.04 (-0.1, 0.2)
Blood bilirubin increased	0 (0.0)	1 (0.04)	-0.04 (-0.1, 0.2)
Hepatic congestion	2 (0.1)	0 (0.0)	0.1 (-0.1, 0.3)
Hepatic enzyme abnormal	1 (0.04)	0 (0.0)	0.01 (-0.1, 0.2)
Hepatic enzyme increased	2 (0.1)	1 (0.04)	0.1 (-0.1, 0.3)
Hepatitis acute	1 (0.04)	0 (0.0)	0.01 (-0.1, 0.2)
Hepatitis toxic	0 (0.0)	1 (0.04)	-0.04 (-0.1, 0.2)
Ischemic hepatitis	3 (0.1)	1 (0.0)	0.1 (-0.1, 0.3)
Liver function test abnormal	1 (0.04)	0 (0.0)	0.01 (-0.1, 0.2)
Liver function test increased	1 (0.04)	0 (0.0)	0.01 (-0.1, 0.2)
Liver injury	3 (0.1)	0 (0.0)	0.1 (-0.1, 0.3)
Multiple organ dysfunction syndrome	1 (0.04)	0 (0.0)	0.01 (-0.1, 0.2)

[1]On treatment at the time of event
[2] MedDRA Preferred Term
Source: adsl.xpt and adae.xpt; OCS Analysis Studio

6.6.6.4. Anemia

The incidence of anemia was 9.7% in the vericiguat group, corresponding to an event rate of 9.4 per 100 patient years and 7.4% in the placebo group, corresponding to an event rate of 7.2 per 100 patient years (Table 45). Subgroup analyses revealed the highest proportion of anemia was reported in the vericiguat group for subjects aged 65 and older, subjects with eGFR ≤ 30 mL/min/1.73 m^2, Black and Multi-racial racial groups, and subjects who used a short-acting nitrate at one or more visits (Figure 17). There was no evidence of a dose-response relationship. Although anemia occurred more frequently in the vericiguat group, the mean Hgb changes from baseline are minimal between treatment groups (Figure 18) and most subjects remained on treatment. There was no difference observed for serious bleeding events between treatment groups.

Reference ID: 4733225

Table 45 Incidence of AESI Anemia, Safety Population, VICTORIA

	Vericiguat (N=2519)	Placebo (N=2515)	Risk Difference (95% CI)
FMQ Anemia, AE[1]	243 (9.7)	185 (7.4)	2.3 (0.8, 3.8)
Anaemia	192 (7.6)	143 (5.7)	1.9 (0.6, 3.3)
Anaemia macrocytic	1 (0.0)	2 (0.1)	0 (-0.2, 0.1)
Anaemia of chronic disease	1 (0.0)	1 (0.0)	0 (-0.1, 0.1)
Autoimmune hemolytic anemia	1 (0.0)	0 (0.0)	0 (0, 0.1)
Blood loss anaemia	3 (0.1)	2 (0.1)	0 (-0.1, 0.2)
Hematocrit decreased	2 (0.1)	2 (0.1)	0 (-0.2, 0.2)
Hemoglobin decreased	8 (0.3)	10 (0.4)	-0.1 (-0.4, 0.3)
Hemolytic anemia	0 (0.0)	1 (0.0)	0 (-0.1, 0)
Hypochromic anaemia	2 (0.1)	2 (0.1)	0 (-0.2, 0.2)
Iron deficiency anaemia	27 (1.1)	19 (0.8)	0.3 (-0.2, 0.8)
Microcytic anaemia	5 (0.2)	2 (0.1)	0.1 (-0.1, 0.3)
Nephrogenic anaemia	1 (0.0)	2 (0.1)	0 (-0.2, 0.1)
Normochromic anaemia	0 (0.0)	1 (0.0)	0 (-0.1, 0)
Normochromic normocytic anaemia	7 (0.3)	3 (0.1)	0.2 (-0.1, 0.4)
Normocytic anaemia	2 (0.1)	1 (0.0)	0 (-0.1, 0.2)
Pancytopenia	6 (0.2)	1 (0.0)	0.2 (0, 0.4)
Pernicious anaemia	0 (0.0)	1 (0.0)	0 (-0.1, 0)
Red blood cell count decreased	4 (0.2)	3 (0.1)	0 (-0.2, 0.3)
FMQ Anemia, SAE[2]	48 (1.9)	28 (1.1)	0.8 (0.1, 1.5)
Anaemia	40 (1.6)	22 (0.9)	0.7 (0.1, 1.3)
Anaemia of chronic disease	43 (1.7)	32 (1.3)	0.4 (-0.3, 1.1)
Autoimmune hemolytic anemia	1 (0.04)	0 (0.0)	0.04 (0.1, 3.0)
Blood loss anaemia	0 (0.0)	1 (0.04)	-0.04 (-0.1, 0.04)
Hemoglobin decreased	1 (0.04)	1 (0.04)	0.0 (-0.1, 0.1)
Iron deficiency anaemia	3 (0.1)	2 (0.1)	0.0 (-0.1, 0.21)
Normochromic normocytic anaemia	1 (0.04)	0 (0.0)	0.04 (0.1, 3.0)
Normocytic anaemia	1 (0.04)	1 (0.04)	0.0 (-0.1, 0.1)
Pancytopenia	3 (0.1)	1 (0.04)	0.06 (-0.1, 0.23)
Anaemia	1 (0.04)	1 (0.04)	0.0 (-0.1, 0.1)

[1] FMQ Broad

[2] FMQ Narrow

Reviewer's Table Source: adsl.xpt and adae.xpt; MAED

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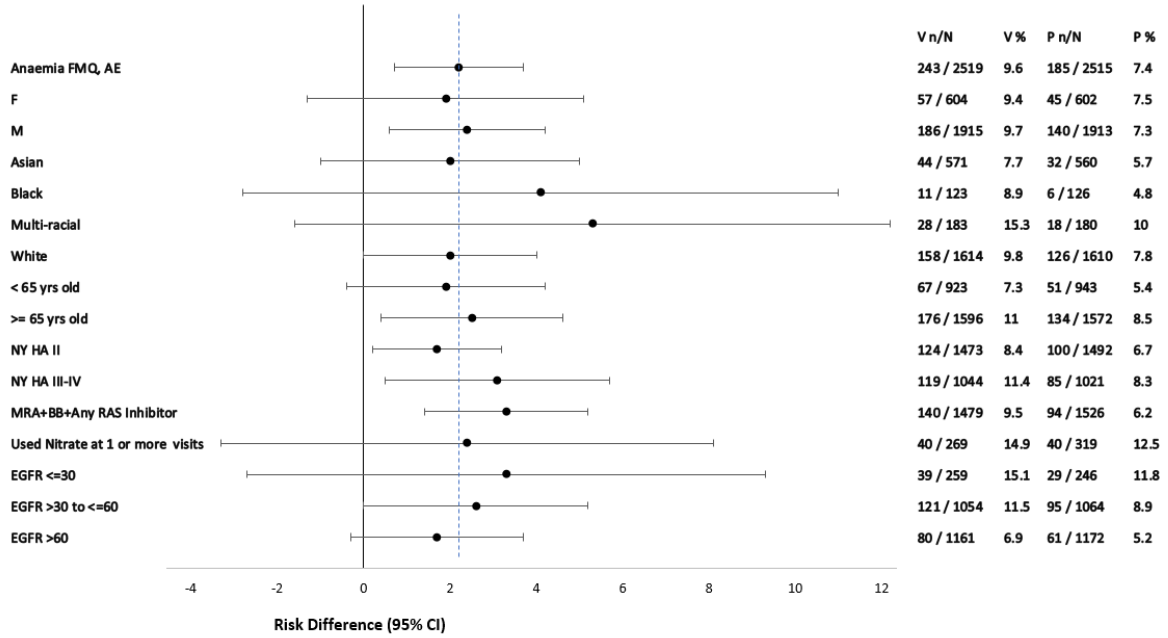
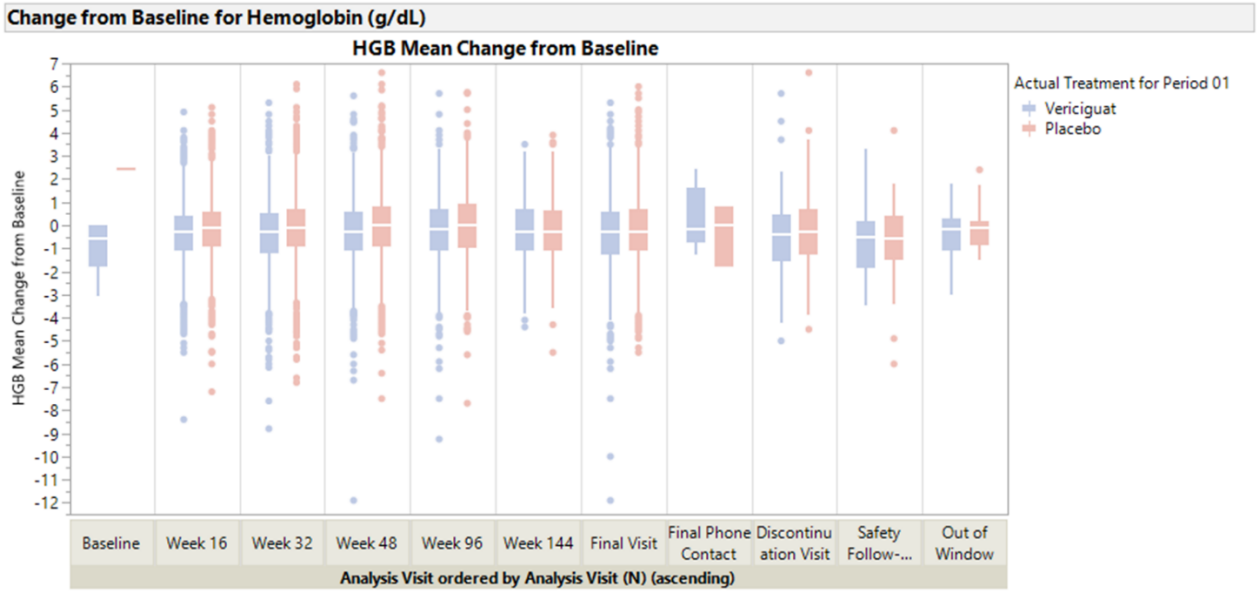
Figure 17 Anemia by Subgroup, Safety Population, VICTORIA, On-Treatment



Reviewer's Figure Source: adae xpt, adsl xpt, adbase xpt, and JMP

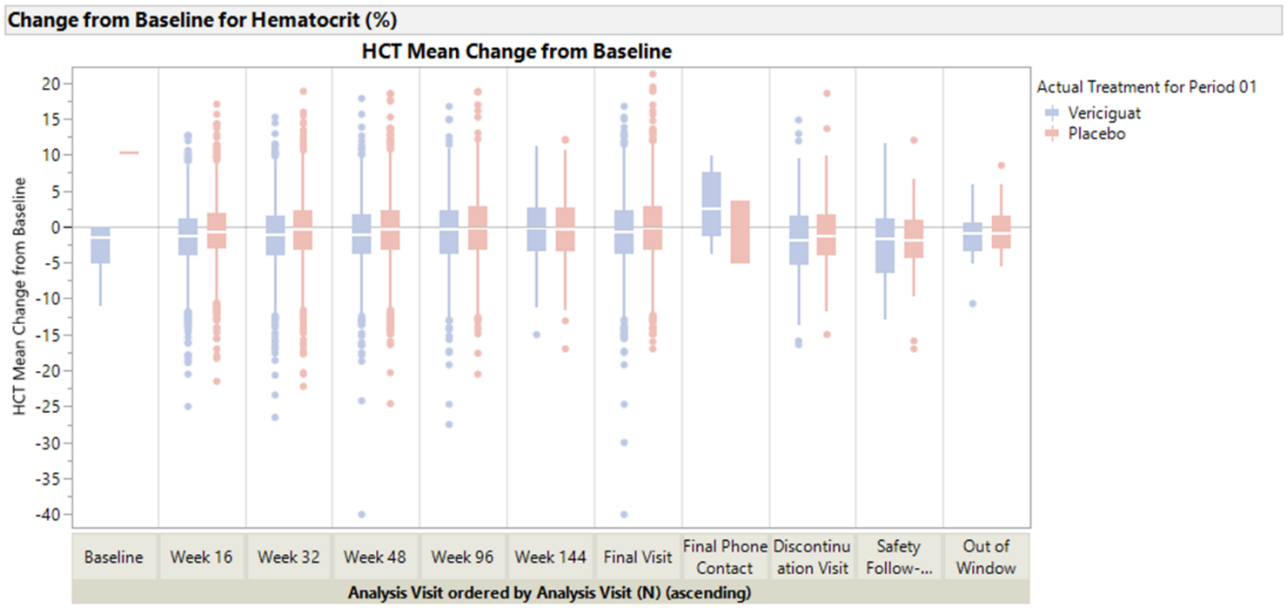
Figure 18. HGB Mean Change from Baseline, Safety Population, VICTORIA, On-Treatment



Reviewer's Figure Source: adsl.xpt, adlb.xpt, and JMP

Reference ID: 4733225

Figure 19. HCT Mean Change from Baseline, Safety Population, VICTORIA, On-Treatment



Reviewer's Figure Source: adsl.xpt, adlb.xpt, and JMP

6.6.7. Laboratory Findings

VICTORIA identified associations between vericiguat use and changes in various laboratory parameters. Isolated AST/ALT elevations (> 3x ULN,> 5x ULN) occurred at similar incidences between treatment arms. Effects on hematology parameters included decreases in hemoglobin; these decreases remained stable throughout the trial and the majority of patients remained on treatment. Additionally, changes to renal lab parameters (increased BUN and creatinine, decreased eGFR) were similar among treatment groups but observed slightly more frequently with vericiguat.

Table 44 Patients Meeting Laboratory Abnormality Criteria, From Baseline Through Week 96, Safety Population, VICTORIA

Laboratory Analysis	Vericiguat N=2519 n (%)	Placebo N=2515 n (%)
Hepatic enzyme elevations		
AST >3X ULN	9 (0.4)	8 (0.3)
AST >5X ULN	2 (0.1)	1 (0)
AST >10X ULN	0 (0)	1 (0)
ALT >3X ULN	13 (0.5)	17 (0.7)
ALT >5X ULN	5 (0.2)	5 (0.2)
ALT >10X ULN	2 (0.1)	1 (0)
TB >2X ULN	59 (2.3)	67 (2.7)
AST or ALT ≥3 × ULN and bilirubin ≥2 × ULN and ALP <2 × ULN[1]	7 (0.3)	5 (0.2)

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Laboratory Analysis	Vericiguat N=2519 n (%)	Placebo N=2515 n (%)
Hemoglobin decrease		
≥ 3 g/dL	131 (5.2)	96 (3.8)
≥ 3 g/dL and < LLN	102 (4.0)	65 (2.6)
≥ 5 g/dL	13 (0.5)	13 (0.5)
≥ 5 g/dL and < LLN	12 (0.5)	10 (0.4)
BUN increase		
Normal Baseline to > ULN	332 (13.2)	353 (14)
Normal Baseline to > 2-fold increase	65 (2.6)	60 (2.4)
Normal Baseline to > 2-fold increase and > ULN	65 (2.6)	56 (2.2)
eGFR decrease		
≥ 25% from Baseline	567 (22.5)	536 (21.3)
≥ 50% from Baseline	73 (2.9)	60 (2.4)
> 60 at Baseline and < 30[2]	11 (0.4)	9 (0.4)
> 60 at Baseline and <15[2]	11 (0.4)	9 (0.4)

Source: Reviewer's analysis [adlb.xpt and JMP]
[1] On treatment at the time of the lab
[2] mL/min/1.73m^2
Abbreviations: LLN, lower limit of normal; N, number of subjects; n, number of subjects with abnormality; ULN, upper limit of normal.

6.7. Review Issues Relevant to the Evaluation of Risk

6.7.1. Embryo-Fetal Toxicity

Issue: Nonclinical data suggests an adverse effect of vericiguat on the developing fetus when administered to a pregnant woman, starting at approximately ≥ 4 times the human exposure at the MRHD of 10mg.

Conclusion: Embryo-fetal toxicity can be adequately mitigated via labeling, including a boxed warning, contraindication for pregnancy, and recommendation to obtain a pregnancy test in females of reproductive potential prior to initiating treatment. Post-marketing data on pregnancy exposure will be collected as a PMR.

Assessment: The intended patient population includes a low number of females of reproductive potential; the majority of HFrEF patients are older females. Pregnant or breastfeeding patients were excluded from VICTORIA and females of reproductive potential were required to use effective contraception. No patients were exposed to vericiguat who were pregnant or breastfeeding during VICTORIA; 1.8% of the patient population were females aged 50 years or younger.

The REMS Oversight Committee (ROC) members determined that labeling can adequately mitigate the risk of embryo-fetal toxicity. The review team and the ROC members discussed prior FDA actions related to risk mitigation for products approved for cardiovascular conditions. Other products used as the standard of care for HFrEF (angiotensin receptor neprilysin inhibitor, angiotensin receptor blockers, ivabradine) include embryo-fetal toxicity risks in labeling, and do

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not have a REMS. Given the benefit of vericiguat on CV death and hospitalization, given that a REMS would represent a significant burden and disincentive to use, and given the small numbers of younger female HFrEF patients who have reproductive potential, the review team decided that imposing a REMS would not be in the best interest of patients.

6.7.2. Bone Metabolism

Issue: Nonclinical data suggests an adverse effect of vericiguat on bone metabolism during growth, most relevant to adolescent and pediatric patients, at doses exceeding the maximally tolerated dose.

Conclusion: Bone effects were not observed in VICTORIA and were not expected given the age of the patient population. A non-clinical PMR will be issued to evaluate developmental toxicity in juvenile rats in order to support dosing for potential studies in a pediatric population.

Assessment: An analysis of the AEs related to bone metabolism in adults did not reveal a signal in VICTORIA. The SMQ for osteoporosis/osteopenia resulted in a greater proportion of AEs in the placebo group (2.4%) versus the vericiguat group (1.7%); there was no imbalance in the AEs in the SMQ for osteonecrosis, with 1.1% in the placebo group and 1.0% in the vericiguat group.

7. Therapeutic Individualization

Please refer to Clinical Pharmacology review for detailed discussions on intrinsic factors and drug interactions. In brief, no dose adjustment is required based on age, renal impairment (eGFR $\geq$ 15 mL/min/1.73m^2) and hepatic impairment (mild to moderate). No dose adjustment is required based on the DDI studies. Concomitant use of vericiguat and PDE5 inhibitors has not been studied in patients with HFrEF and is therefore not recommended due to the potential increased risk for symptomatic hypotension. Vericiguat is contraindicated in patients with concomitant use of other sGC stimulators, such as riociguat.

7.1. Pediatric Labeling/Plans for Pediatric Drug Development

An Agreed iPSP was issued on December 14, 2016 in which the applicant sought a full waiver for all pediatric age groups for the reason that studies are impossible or highly impractical. However, approaching the end of the review cycle, the applicant determined that the study may be feasible and proposed a single phase 2/3 study to satisfy both PREA requirement and a Written Request. The applicant is seeking partial waiver for age 0 to $\leq$ 28 days and deferral for age > 28 days to < 18 years.

The Division has a safety concern based on mechanistic considerations and nonclinical toxicology studies, which suggest a potential for adverse effects of vericiguat on bone

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(hyperostosis), particularly in pediatric patients. The clinical risk for the occurrence of hyperostosis appears to be highest during periods of rapid bone growth (e.g., late third trimester and early childhood). The Division does not think that the submitted pre-clinical assessments on bone effects are adequate and sufficient to support the safety of conducting clinical pediatric studies with vericiguat at this time. Based on DCN discussions with the Division of Pediatrics and Maternal Health (DPMH) and a follow-up meeting with the Pediatric Review Committee (PeRC) on January 5, 2021, DCN will defer pediatric clinical studies pending the availability of additional pre-clinical studies to be performed as a PMR to identify which if any pediatric age groups may be appropriate to study (see section 15 Postmarketing Requirement and Commitments). The deferral will be converted to a partial or a complete waiver based on those results.

7.2. Pregnancy and Lactation

Based on data from animal reproduction studies, vericiguat can cause fatal harm when administered to a pregnant woman and is contraindicated during pregnancy. There are no available data with vericiguat use in pregnant women.

There are no data on the presence of vericiguat in human milk, the effects on the breastfed infant, or the effects on milk production.

8. Human Subjects Protections/Clinical Site and Other GCP Inspections/Financial Disclosure

The applicant has adequately disclosed financial arrangements with clinical investigators and VICTORIA appears to have been conducted in compliance with U.S. regulations pertaining to Good Clinical Practice. Three foreign sites (i.e., #1614 in Eastern Europe, #1912 in Africa and #0501 in Latin America) that have the highest total risk for inspection and enrolled large numbers of study subjects were selected for OSI inspections to verify the quality of conduct of the study (see Appendix III.13).

9. Advisory Committee Summary

An advisory committee meeting was not convened to discuss this application. The study design, endpoints, and statistical plan were typical of studies for this indication, and the results were clear and non-controversial. No safety issues were identified that might have benefitted from a public discussion.

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III. Appendices

10. Summary of Regulatory History

The original IND was submitted on June 17th, 2013 and FDA granted Fast-Track destination on June 23rd, 2014. The IND was transferred from Bayer to Merck on February 1st, 2016. The NDA was submitted on May 21st, 2020. The key regulatory history is summarized in the table below:

Table 45 Summary of Key Regulatory History

Source	Advice from Agency
May 9, 2013 Pre-IND Meeting Minutes	The applicant was planning two phase IIb studies to choose appropriate doses for two planned phase III trials (i.e., one in HFrEF and one in HFpEF). The applicant requested the meeting to discuss the clinical development program and the proposed indication [redacted] (b) (4) *Proposed Phase IIb studies* Agency agreed with the overall design of the study with 4 parallel trial arms (placebo and three active doses) and the titration scheme. Agency recommended that the applicant characterize the PK and BP effects in the target population prior to phase 2 studies due to safety concern. *Proposed Phase III studies* Agency did not object to the proposed endpoint but stated that discussion of endpoint should be deferred until at least some clinical studies of vericiguat in the target population have been conducted. Agency stated that two trials that both met the pre-defined statistical analyses, [redacted] (b) (4) If one study fails, approval may be possible for the population enrolled in the successful trial depending on the specific outcome.
November 18, 2015 End of Phase 2 (EOP2) Meeting	The applicant desired to discuss the all aspects of clinical development, and specifically a strategic change targeting approval based on a single phase 3 study VICTORIA in patients with HFrEF. *Clinical Pharmacology* Agency agreed that the clinical development program for clinical pharmacology studies should be adequate. Agency recommended that the applicant conduct a sacubitril/valsartan pharmacodynamic interaction study prior to the start of phase 3.

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	Proposed Phase III study in patients with HFrEF *Dose* Agency agreed that the proposed dose of 10 mg is reasonably safe but recommended that a higher dose be studied. Given the uncertainty about the relationship between a modest effect of NT-proBNP (shown in phase IIb study) and CV outcomes, Agency stated that studying a higher dose would be prudent to increase the chance of identifying an efficacious dose. *Study Endpoints* Agency agreed with the proposed primary efficacy endpoint and provided advice on the proposed secondary endpoints. Agency stated that if the applicant seeks labeling that includes secondary endpoints, they will need to control Type-I error rates and plan a sequential analysis. Agency also stated that a statistically positive result would not result in an all-cause mortality claim. Agency expressed concern about a frequency analysis for HF hospitalization and thought a more relevant outcome would be days alive and out of hospital. *Standard of Care* Agency expressed concerns regarding regional differences in adopting new therapies (e.g. sacubitril/valsartan), and the use of indicated device therapies for HFrEF. Agency advised the applicant that life-saving pharmacologic therapies should not be altered for the sake of initiating or dose escalating vericiguat and the optimization of background therapies should be documented. In addition, the Agency had the following comments: • It will be important that the safety and effectiveness of vericiguat administration on a background of sacubitril/valsartan be unequivocally defined, given that the use of the latter can be reasonably expected to increase in the future. • Recent clinical trials have demonstrated a remarkable variation in the use of indicated device therapies for HFrEF, specifically the ICD, CRT, and CRT-D, all of which impact mortality and/or hospitalization for worsening heart failure in an important way. • For both background pharmacologic and device therapies for HFrEF, it will be important that the utilization of these therapies reflect contemporary management of HFrEF in US heart failure centers, and that benefit of vericiguat is demonstrated in that setting. *Proposed indication giving the enrichment criteria* Agency stated a broader claim would be granted would depend on whether analyses suggest that efficacy is importantly different in those who are the more severely ill/symptomatic (e.g. with respect to baseline levels of NT-proBNP).

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	Exclusion criterion regarding nitrite use The applicant believed use of short-acting nitrates is safe based on DDI studies in animals and healthy volunteers and should be allowed in the VICTORIA though long-acting nitrates use will not be allowed. Agency believed that running nitrate DDI studies in parallel to the phase 3 study is suboptimal Agency recommended ascertainment of adverse events caused by vericiguat and nitrate use should be prespecified and protocol-driven. *Statistical Analysis* Agency stated that because the p -value for the primary efficacy analysis needs to be substantially less than 0.05 for the drug to be approved, the nominal significance levels at the interim analysis and the final analysis need to be adjusted accordingly. Agency provided further comments on interim analysis on the advice letter dated January 11, 2016.
January 11, 2016 FDA Advice Letter (additional statistical analysis plan comments post-EOP2 meeting)	Agency stated that the VICTORIA trial must be successful at a *p*-value <0.01 (two sided) if the applicant proposes to conduct a single confirmatory trial. Agency recommended that the interim analysis to stop by the trial should be based solely on an effect on CV death.
June 29, 2016 FDA Information Request	Agency issued information request to provide additional comments and recommendations after the EOP2 meeting. *QT evaluation* Agency expected that a similar approach to TQT evaluation would be taken for vericiguat as was done for riociguat. Further QT evaluation in the phase 3 trial would be required. *PD evaluation for nitrate and PDE5-I interactions* Agency advised the applicant to include information regarding this potential interaction in the draft ICF and revise the language in the IB.
December 14, 2016 Agreed iPSP	The applicant was seeking a full waiver for all pediatric age groups for the reason that studies are impossible or highly impractical.
February 3, 2020 PreNDA Topline Results	The Agency agreed that the presented topline data would support and NDA submission. The Agency suggested that the indication of (b) (4) be clarified. The Agency noted the unfavorable results in subjects with the highest baseline NT-proBNP and suggested analyses with NT-proBNP as a continuous variable.

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	The Agency requested the following analyses of efficacy for inclusion in the NDA submission • Primary efficacy based on investigator assessment of outcomes • Primary efficacy incorporating urgent clinic visits • Quality of life outcomes as a function of baseline NYHA class
February 20, 2020 PreNDA Meeting	The Agency agreed with the content and format of the proposed package to support the review of the vericiguat NDA.

Source: Reviewer's table

11. Trial Design: Additional Information and Assessment

11.1. Protocol Amendments

The clinical protocol was amended five times (2 general amendments and 3 site-specific amendments). An overview of each amendment can be seen in the table below.

Table 46 Overview of Protocol Amendments

Amendment No. and Date	Summary of Significant Changes
Amendment 1 6/15/2016	Exclusion criteria were added to: • Exclude subjects with interstitial lung disease from the trial • Exclude subjects who are breastfeeding or plan to breastfeed during the course of trial.
Amendment 2 (Country-specific Japan) 6/15/2016	Change was made based on a request from Japanese Pharmaceuticals and Medical Device Agency: • Added a visit 4 weeks after up-titration to 10 mg dose • The protocol was revised to allow for optional additional unscheduled visits at the discretion of the investigator • Protocol revised to indicate that only Urgent HF visits and HF-related hospitalization are exempted from expedited SAE reporting • eGFR will be calculated using the Japanese equation
Amendment 3 (Country-specific Germany and Czech Republic) 9/21/2016	Modifications and clarifications were made regarding two exclusion criteria • "Has known allergy or sensitivity to any sGC stimulator" criterion also applies to subjects have a prior history of hypersensitivity reaction to the active substance of the investigational product or any of its constituents

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	• Subjects who are pregnant or plan to become pregnant during the trial are excluded from the trial
Amendment 4 12/20/2017	Changes were made to address FDA recommendation regarding futility analysis: • Futility analysis will be performed at 75% of CV death events
Amendment 5 (Country-specific Japan) 2/15/2018	The same changes in amendment 4 regarding futility analysis approach and futility bounds were added Additional changes added to clarify inclusion/exclusion criteria

Source: Reviewer's table

11.2. Endpoint Event Identification and Triggering Process

Potential efficacy endpoint events were electronically identified ("auto-triggered") for adjudication by the CEC using programmatic algorithm triggering when events were reported in the required eCRF (InForm). If the potential event was on or after the subject's randomization visit (Visit 2), then an adjudication reference ID number was generated. The adjudication process was triggered depending on the presence of an adjudication reference ID, and the clinical event definitions aligned with the established CEC charter.

In addition to the automated triggering process, additional steps were taken by the CEC and the applicant study team to ensure all potential endpoints were triggered for adjudication. The CEC reviewed verbatim site comments on all endpoint event eCRFs for any evidence of an additional event. The applicant study team performed medical monitoring of InForm data across relevant eCRFs to ensure any potential endpoints were recorded appropriately on the endpoint eCRFs. The applicant also performed source document review and verification for all site reported endpoints.

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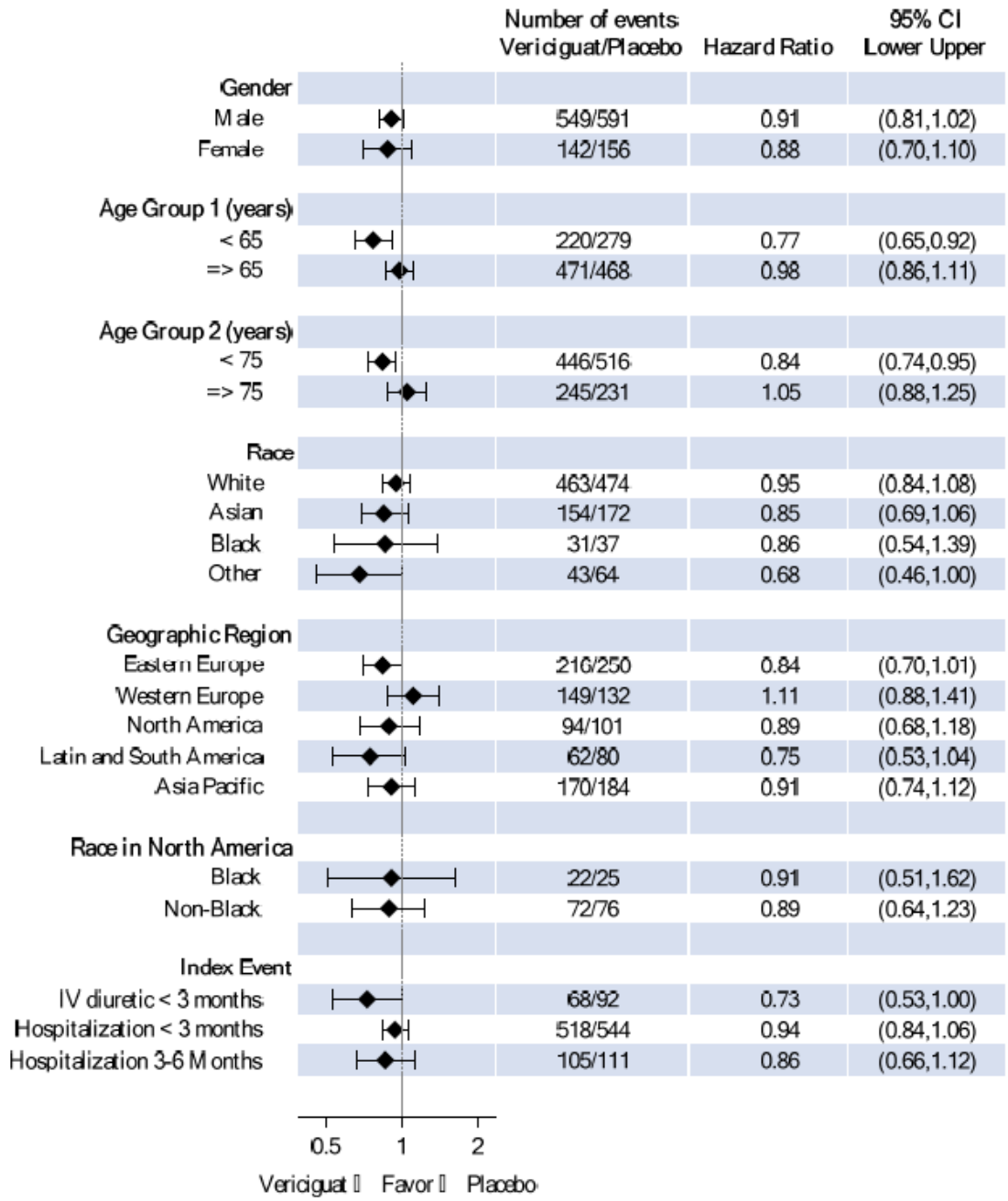
12. Efficacy Assessment Additional Information and Assessment

12.1. Subgroup Analysis of First HF Hospitalization

Figure 17 Forest Plot for Subgroup Analysis of First HF Hospitalization (Prespecified Subgroups), ITT Population, VICTORIA



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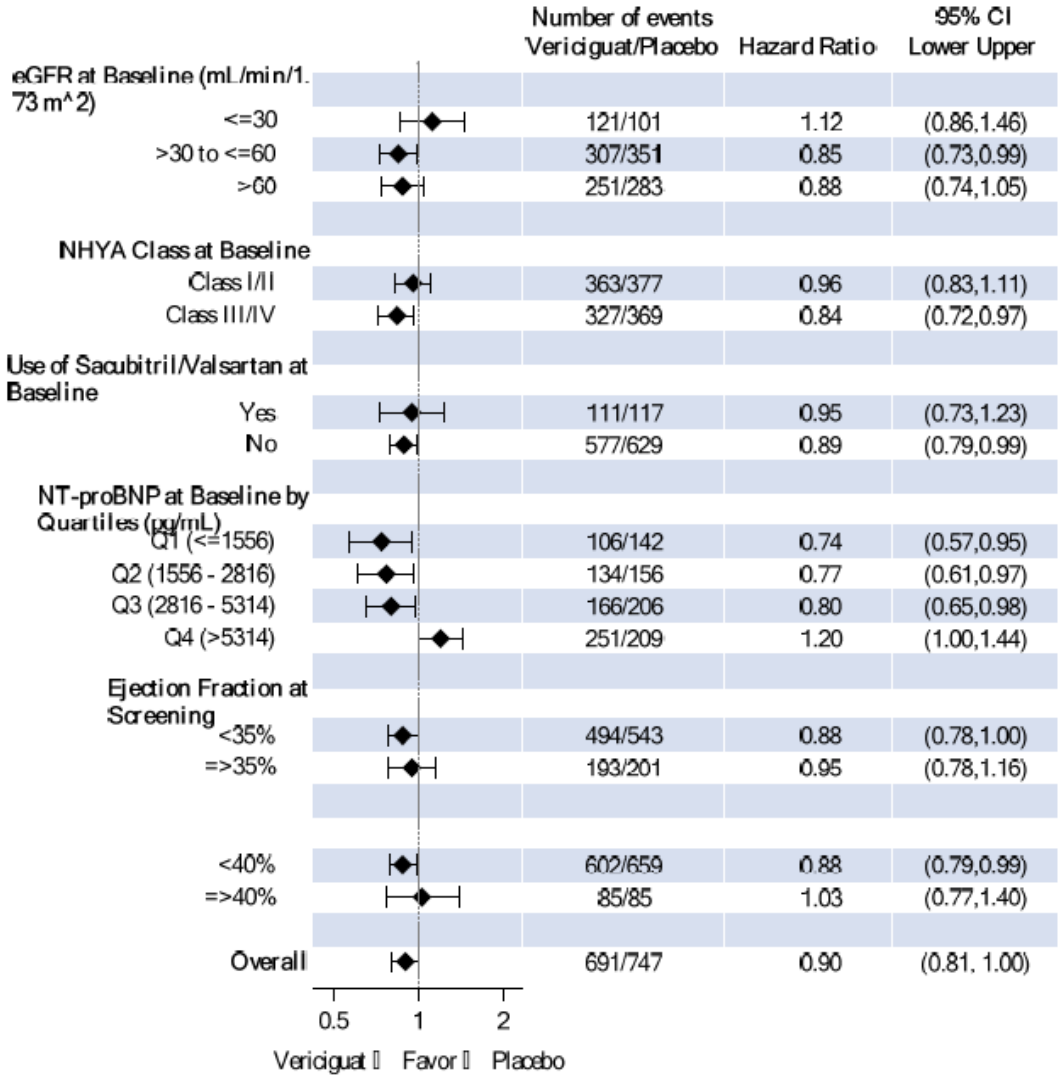
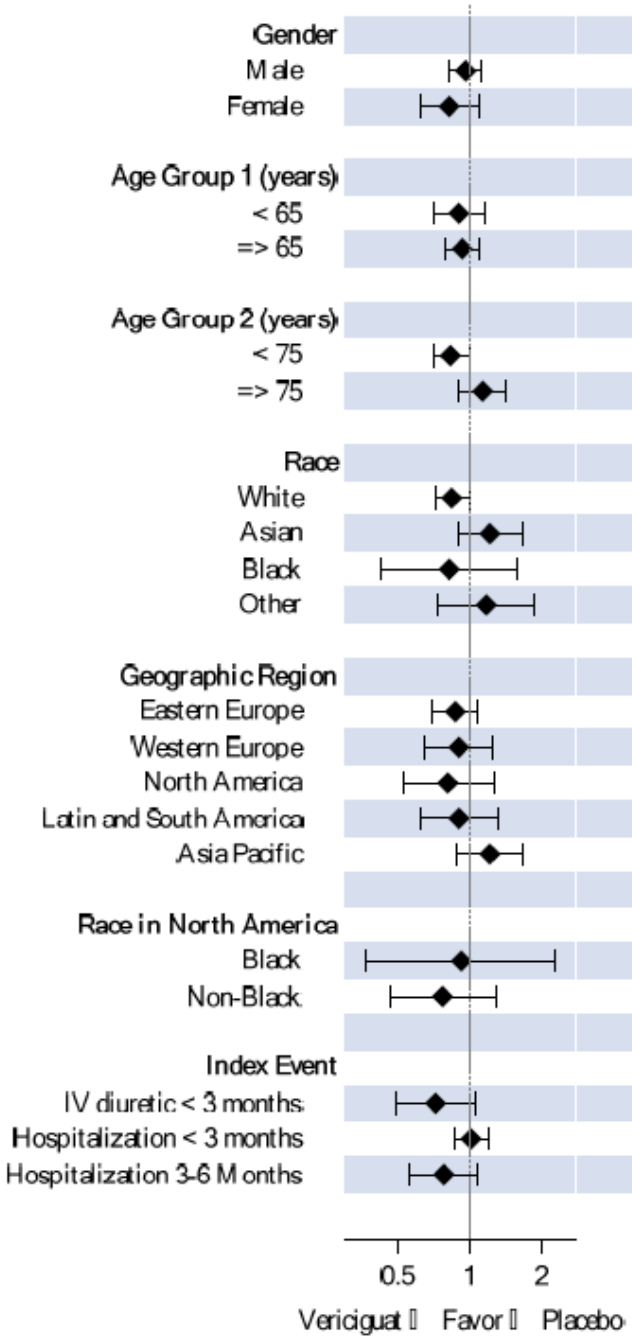


Source: The applicant's CSR, Figure 11-6

12.2. Subgroup Analysis of CV Death

Figure 18 Forest Plot for Subgroup Analysis of CV Death (Prespecified Subgroups), ITT Population, VICTORIA



	Number of events Vericiguat/Placebo	Hazard Ratio	95% CI Lower Upper
Gender			
Male	330/342	0.96	(0.82,1.12)
Female	84/99	0.82	(0.62,1.10)
Age Group 1 (years)			
< 65	126/142	0.90	(0.71,1.15)
=> 65	288/299	0.93	(0.79,1.10)
Age Group 2 (years)			
< 75	253/301	0.83	(0.71,0.99)
=> 75	161/140	1.13	(0.90,1.41)
Race			
White	273/315	0.84	(0.72,0.99)
Asian	88/71	1.21	(0.89,1.66)
Black	16/21	0.82	(0.43,1.57)
Other	37/34	1.17	(0.73,1.86)
Geographic Region			
Eastern Europe	164/185	0.87	(0.70,1.07)
Western Europe	71/78	0.90	(0.65,1.24)
North America	37/44	0.81	(0.53,1.26)
Latin and South America	55/61	0.90	(0.63,1.30)
Asia Pacific	87/73	1.21	(0.88,1.65)
Race in North America			
Black	9/10	0.92	(0.37,2.25)
Non-Black	28/34	0.77	(0.47,1.28)
Index Event			
IV diuretic < 3 months	46/63	0.72	(0.49,1.05)
Hospitalization < 3 months	303/300	1.01	(0.86,1.19)
Hospitalization 3-6 Months	65/78	0.78	(0.56,1.08)

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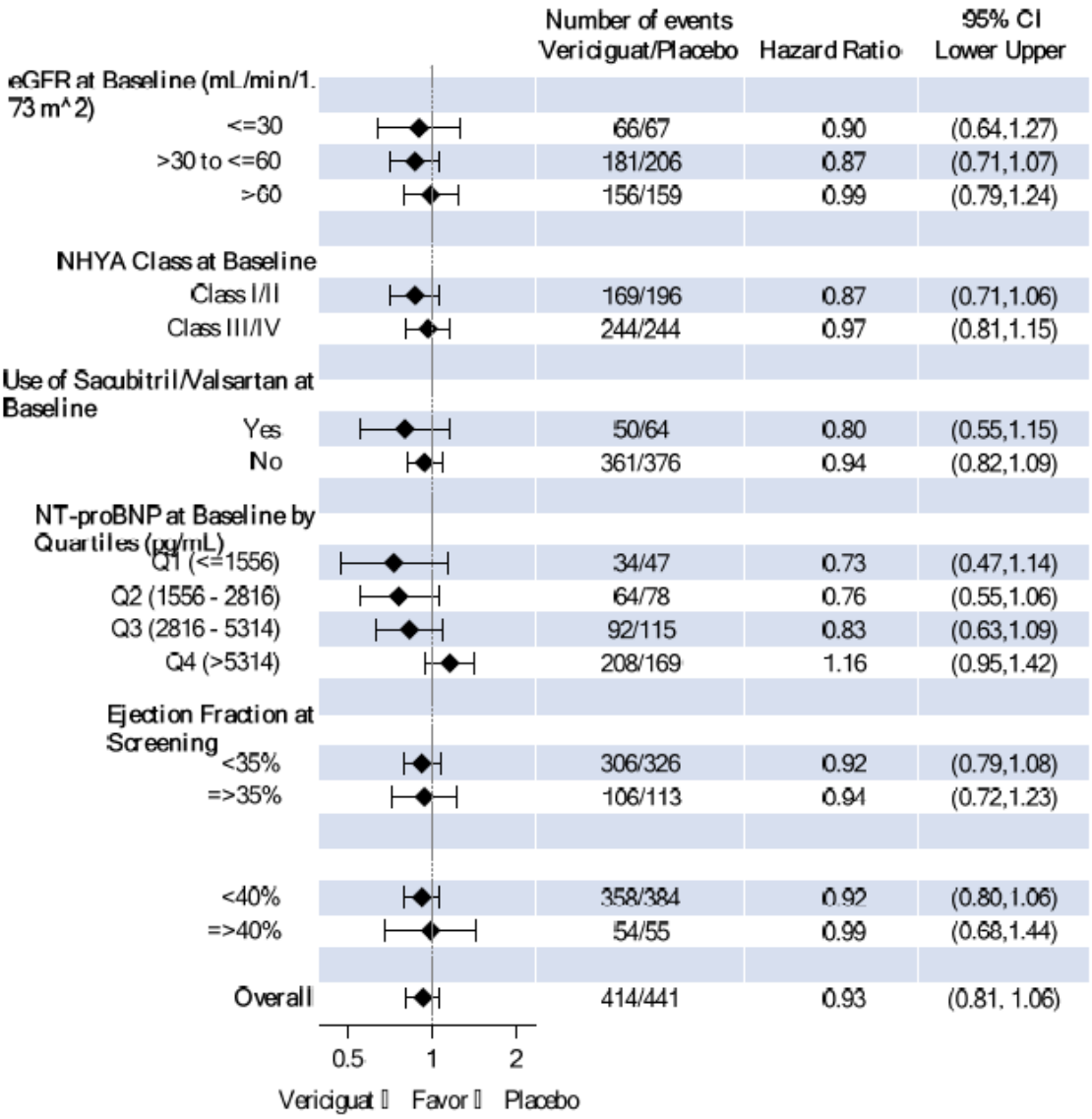

Source: The applicant's CSR, Figure 11-4

12.3. On Treatment CV Deaths by Baseline NT-proBNP

Table 47 Causes of On-Treatment Cardiovascular Death by Baseline NT-proBNP Quartile, ITT Population, VICTORIA

	Placebo				Vericiguat			
	Q1 (<=1556) (N=604)	**Q2 (1556 - 2816) (N=589)**	**Q3 (2816 - 5314) (N=613)**	**Q4 (>5314) (N=585)**	**Q1 (<=1556) (N=599)**	**Q2 (1556 - 2816) (N=613)**	**Q3 (2816 - 5314) (N=586)**	**Q4 (>5314) (N=616)**
CV death (on treatment)[a]	21 (3.5)	53 (9.0)	63 (10.3)	85 (14.5)	18 (3.0)	33 (5.4)	53 (9.0)	113 (18.3)
Sudden Cardiac Death	7 (1.2)	18 (3.1)	24 (3.9)	23 (3.9)	8 (1.3)	7 (1.1)	24 (4.1)	44 (7.1)
Heart Failure	9 (1.5)	20 (3.4)	25 (4.1)	34 (5.8)	3 (0.5)	14 (2.3)	17 (2.9)	39 (6.3)
Undetermined Cause Of Death	2 (0.3)	10 (1.7)	9 (1.5)	23 (3.9)	7 (1.2)	7 (1.1)	8 (1.4)	19 (3.1)
Other Cardiovascular Event	1 (0.2)	3 (0.5)	0	1 (0.2)	0	3 (0.5)	2 (0.3)	5 (0.8)
Myocardial Infarction	0	0	4 (0.7)	3 (0.5)	0	2 (0.3)	2 (0.3)	3 (0.5)
Stroke	2 (0.3)	2 (0.3)	1 (0.2)	1 (0.2)	0	0	0	3 (0.5)

[a]CV death occurred with 14 days after the last dose of study drug
Source: Reviewer's Table datasets: adsl, adbase, and adeff, OCS Analysis Studio, Custom Table Tool

12.4. Multivariate Analysis for Efficacy Outcomes

12.4.1. CV Mortality

Table 48 Parameter Estimates and Estimated Hazard Ration from The Multivariate Model for CV Mortality for Important Covariates*

Model covariates	**Parameter estimates**	**Hazard Ratio**	**95% CI**	***p*-value**
Age[a]	0.0077	1.08	(1.01, 1.15)	0.02
LVEF[b]	-0.009	0.96	(0.91, 1.00)	0.04
NYHA (Class III and IV vs. Class I & II)	0.51	1.66	(1.44, 1.92)	< 0.0001
Triple Therapy (Y vs. N)	-0.22	0.80	(0.69, 0.93)	0.003

[a] HR for age was estimated with a unit of 10
[b] HR for baseline EF was estimated with a unit of 5
* Estimated HR by baseline device use and by NT-proBNP was shown in **Figure 9** and **Table 32**
Source: Reviewer's analysis, datasets: adsl, adbase, adsoch and adttec.

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12.4.2. First HF Hospitalization

Table 49 Estimated Hazard Ratios by Baseline NT-proBNP from The Multivariate Model for First HF Hospitalization

NT-proBNP (pg/mL)	Hazard Ratio (Vericiguat vs. Placebo)	95% CI
1000	0.70	(0.56, 0.87)
2000	0.72	(0.60, 0.87)
3000	0.83	(0.72, 0.95)
4000	0.93	(0.80, 1.08)
5000	1.00	(0.84, 1.18)
6000	1.04	(0.88, 1.22)
7000	1.07	(0.90, 1.23)
8000	1.09	(0.92, 1.29)
9000	1.10	(0.94, 1.30)
10000	1.12	(0.94, 1.32)

Source: Reviewer's analysis, datasets: adsl, adbase, adsoch and adttec.

Table 50 Parameter Estimates and Estimated Hazard Ration from the Multivariate Model for First HF Hospitalization for Important Covariates

Model covariates	Parameter estimates	Hazard Ratio	95% CI	*p*-value
Sex (Male vs. Female)	0.19	1.21	(1.06, 1.39)	0.004
BMI[a]	0.02	1.13	(1.08, 1.18)	<0.0001
eGFR[b]	-0.005	0.95	(0.93, 0.97)	<0.0001
LVEF[a]	-0.006	0.97	(0.94, 1.00)	0.08
NYHA (Class III and IV vs. Class I & II)	0.26	1.30	(1.17, 1.46)	< 0.0001
Triple Therapy (Y vs. N)	-0.10	0.90	(0.81, 1.01)	0.07
Device (Y vs. N)	0.28	1.32	(1.18, 1.49)	< 0.0001

[a] HR for BMI or LVEF was estimated with a unit of 5
[b] HR for eGFR was estimated with a unit of 10
Source: Reviewer's analysis, datasets: adsl, adbase, adsoch and adttec.

Reference ID: 4733225

12.4.3. Primary Efficacy Endpoint

Table 51 Estimated Hazard Ratios by Baseline NT-proBNP and by Baseline Device Use from the Multivariate Model for the Primary Efficacy Endpoint

NT-proBNP (pg/mL)	Device		No Device	
	Hazard Ratio (Vericiguat vs. Placebo)	95% CI	Hazard Ratio (Vericiguat vs. Placebo)	95% CI
1000	0.64	(0.51, 0.81)	0.77	(0.63,0.95)
2000	0.63	(0.51, 0.78)	0.76	(0.63, 0.91)
3000	0.73	(0.61, 0.86)	0.88	(0.76, 1.01)
4000	0.82	(0.69, 0.98)	0.99	(0.85, 1.15)
5000	0.88	(0.73, 1.06)	1.06	(0.90, 1.25)
6000	0.92	(0.76, 1.11)	1.11	(0.94, 1.31)
7000	0.95	(0.78, 1.15)	1.14	(0.97, 1.34)
8000	0.97	(0.80, 1.17)	1.16	(0.99, 1.37)
9000	0.98	(0.81, 1.18)	1.18	(1.01, 1.38)
10000	0.99	(0.82, 1.19)	1.19	(1.02, 1.40)

Source: Reviewer's analysis, datasets: adsl, adbase, adsoch and adttec.

Table 52 Parameter Estimates and Estimated Hazard Ration from The Multivariate Model for The Primary Efficacy Endpoint for Important Covariates

Model covariates	Parameter estimates	Hazard Ratio	95% CI	P-value
Sex (M vs. F)	0.17	1.19	(1.06, 1.33)	0.004
BMI[a]	0.017	1.09	(1.04, 1.14)	< 0.0001
eGFR[b]	-0.003	0.97	(0.95, 0.99)	0.009
LVEF[a]	-0.005	0.98	(0.95, 1.01)	0.097
NYHA (Class III and IV vs. Class I & II)	0.32	1.38	(1.25, 1.52)	< 0.0001
Triple Therapy (Y vs. N)	-0.16	0.85	(0.77, 0.94)	0.002

[a] HR for BMI or LVEF was estimated with a unit of 5
[b] HR for eGFR was estimated with a unit of 10
Source: Reviewer's analysis, datasets: adsl, adbase, adsoch and adttec.

Reference ID: 4733225

13. Data Integrity-Related Consults (OSI, Other Inspections)

The Division requested OSI to inspect 3 foreign sites that have the highest total risk for inspection and enrolled large numbers of study subjects. Two non-ICH sites have been inspected via a remote regulatory inspection as an alternative to the on-site inspection due to the COVID-19 pandemic. These reviews are limited in scope due to the logistical constraints of the information exchange. OSI did not identify significant deficiencies among the available records. The Division agreed to cancel the inspection for the third site in Poland because a remote inspection cannot be conducted under the General Data Protection Regulation in the region and the on-site inspection was not feasible during the COVID-19 pandemic.

14. Labeling Summary of Considerations and Key Additional Information

Labeling negotiations with the applicant are ongoing. The two major labeling issues relevant to the clinical review are:

- how to label the significant efficacy subgroup findings related to CV death and baseline NT-proBNP, and
- how to label the embryo-fetal toxicity.

The applicant was originally silent about the unfavorable efficacy results in the highest baseline NT-proBNP quartile. After the first round of labeling negotiations, the applicant agreed that these results should be described further in Section 14.

The DPMH was consulted to address the risk of the embryo-fetal toxicity and review the related sections of labeling. The DPMH recommended similar labeling language consistent with other products, i.e., riociguat regarding the pregnancy risk, which includes a boxed warning for females of reproductive potential and recommended pregnancy testing prior to initiation of treatment and a contraindication for pregnancy.

15. Postmarketing Requirements and Commitments

The Division will issue a PMR to monitor for potential pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Given the limited clinical data in humans and the absence of a REMS, there is a need for long term data collection and analysis to monitor and characterize the risk of embryo-fetal toxicity of vericiguat in real world settings. Such knowledge will inform regulatory actions to ensure the safe use of vericiguat and prevent maternal and fetal harm. The DPMH recommended the applicant conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to vericiguat during pregnancy, including fetal effects, and neonate/infant outcomes will be assessed through at least the first year of life. The study will collect information for a minimum of 10 years; results will be analyzed separately and reported descriptively with the interim and final study reports.

Reference ID: 4733225

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The Division is also planning to issue a PREA PMR to evaluate the efficacy and safety of vericiguat in pediatric patients with HF due to systemic left ventricular systolic dysfunction consistent with dilated cardiomyopathy pending a competent nonclinical assessment.

A related but separated PMR will be issued to conduct nonclinical toxicity studies in juvenile rats to evaluate developmental toxicity including an assessment of the effects of vericiguat on appendicular and axial bone development, as well as cranial nerve foramina, to support dosing in human down to 28 days old. A pediatric study will move forward only if nonclinical data supports the safety of vericiguat in the pediatric population, or subgroups of that population. There will be ongoing discussions between the Division, DPMH and PeRC about the design of the proposed pediatric study and a formal PMR.

16. Financial Disclosure

Table 53. Covered Clinical Studies: [VICTORIA]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 3425		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 2 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒[a] (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 162		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

[a] There were no steps specifically taken for the 6 investigators, accounting for a total of 8 sites (total N =51) to minimize bias. However, VICTORIA was a randomized, double-blind, multi-center trial, and the impact of these small sites on the overall results is minimal. Hence, we do not believe that the stated financial interests were a source of bias in VICTORIA.

17. References

1. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional and national incidence, prevalence and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016.

Reference ID: 4733225

2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2013 Oct 15;62(16):e147-239.
3. Tsao CW, Lyass A, Enserro D, Larson MG, Ho JE, Kizer JR, et al. Temporal Trends in the Incidence of and Mortality Associated With Heart Failure With Preserved and Reduced Ejection Fraction. JACC Heart Fail. 2018;6(8):678-85.
4. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, et al. 2016 ACC/AHA /HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Cardiac Fail. 2016;22:659-69
5. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Granger CB, Hammill SC, Hlatky MA, Joglar JA, Kay GN, Matlock DD, Myerburg RJ, Page RI. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2018;72:e91-220.

18. Review Team Acknowledgements

Table 54. Reviewers of Interdisciplinary Assessment

Role	Name(s)
Regulatory Project Manager	Alexis Childers
Nonclinical Reviewer	Elizabeth Hausner
Nonclinical Team Leader	Xuan Chi
Office of Clinical Pharmacology Reviewer(s)	Anusha Ande/Girish Bende
Office of Clinical Pharmacology Team Leader(s)	Sudharshan Hariharan/Justin Earp
Clinical Reviewer	Tzu-Yun McDowell/Selena DeConti
Clinical Team Leader	Preston Dunnmon
Statistical Reviewer	Fanhui Kong
Statistical Team Leader	Jialu Zhang
Cross-Disciplinary Team Leader	Preston Dunnmon
Division Director (OB)	Mark D Rothmann
Division Director (DCN)	Norman Stockbridge
Office Director (signatory)	Ellis Unger

Reference ID: 4733225

Table 55. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Zhengfu Wang/Dan Berger/Min Sung/Teng Xu
OSI	Tina Suyoung Chang
OSE/DEPI	Yan Li
OSE/DMEPA	Max Straka
OSE/DRM	Theresa Ng

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRM=Division of Risk Management

Reference ID: 4733225

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/s/

ALEXIS T CHILDERS
01/19/2021 12:18:39 PM

FANHUI KONG
01/19/2021 12:46:01 PM

JIALU ZHANG
01/19/2021 12:47:55 PM

MARK D ROTHMANN
01/19/2021 02:40:51 PM
I concur

TZU-YUN C MCDOWELL
01/19/2021 02:44:21 PM

SELENA D READY
01/19/2021 02:45:50 PM

PRESTON M DUNNMON
01/19/2021 02:52:02 PM

NORMAN L STOCKBRIDGE
01/19/2021 03:12:23 PM

ELLIS F UNGER
01/19/2021 03:16:33 PM

Memorandum

Date: October 28, 2020

From: E.A. Hausner

To: Xuan Chi

CC: Todd Bourcier

Alexis Childers

Subject: Vericiguat embryo-fetal development

Background

The primary nonclinical reviewer and the sponsor had different interpretations of the rabbit embryo-fetal development study. The matter was referred to the Pharmacology Toxicology Reproductive Toxicology Subcommittee (RTS) for their interpretation. The RTS arrived at an interpretation similar to that of the nonclinical reviewer. The differences of interpretation, supporting arguments and suggested labeling edits regarding the embryofetal effects have been summarized in N214377EFDsummary.consult (entered into DARRTS October 26, 2020). This addendum to the primary NDA review has received secondary concurrence from Dr. Chi and tertiary concurrence from Dr. Bourcier.

Reference ID: 4693710

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/s/

ELIZABETH A HAUSNER
10/28/2020 03:53:53 PM

XUAN CHI
10/28/2020 04:09:11 PM

TODD M BOURCIER
10/28/2020 06:10:23 PM
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA214377
Supporting document/s:	0026
Applicant's letter date:	October 5, 2020
Product:	Vericiguat BAY1021189
Indication:	Heart failure
Applicant:	Merck
Review Division:	DPT for OCHEN
Reviewer:	E.A. Hausner
Supervisor/Team Leader:	Xuan Chi
Division Director:	Todd Bourcier
Project Manager:	Alexis Childers

Template Version: September 1, 2010 (Modified by DCRP: June 10, 2013)

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 214377 are owned by Merck or are data for which Merck has obtained a written right of reference.
Any information or data necessary for approval of NDA214377 that Merck does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA214377.

Reference ID: 4691893

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Reference ID: 4691893

1 Executive Summary

1.1 Introduction (and Clinical Rationale)

Vericiguat is a soluble guanylate cyclase stimulator developed for chronic heart failure. Soluble guanylate cyclase stimulates production of cGMP, a signaling molecule that is involved in vascular smooth muscle relaxation, cardiac contractility, and cardiac remodeling. It is proposed that vericiguat can help remediate deficiencies in intracellular cGMP levels thus improving myocardial and vascular function via vasodilation and decreasing cardiac afterload.

1.2 Brief Discussion of Nonclinical Findings

The primary nonclinical reviewer interpreted the embryo-fetal development studies (EFD) to indicate fetal toxicity manifested as malformations in the rabbit study and variations in the rat study related to treatment with vericiguat. The sponsor challenged this interpretation on the premise that the malformations were within the range of the historical controls.

The primary reviewer found the historical control data for the rabbit study to be inappropriate, with the majority originating more than 5 years prior to the conduct of the studies. In addition, the rabbit strain used in the study was different from the strain used in the historical studies. Overall, there was no relevant historical data to support the sponsor's contention. The matter was presented to the Pharmacology Toxicology Coordinating Committee Reproductive Toxicology Subcommittee (RTS) for consultation.

The RTS interpreted the results of the rabbit EFD as demonstrating treatment-related malformations. This was based on several factors. The rabbit pilot EFD (T100654-6) noted that 2 out of 3 dams aborted at 10 mg/kg. The one remaining litter had "one fetus with common origin of innominate artery and left carotid artery at visceral evaluation." For the definitive GLP rabbit EFD, rare malformations were observed in 4 out of 10 litters. In addition to the cardiac and major vessel malformations, one litter had a fetus with a missing kidney and ureter, and isolated part of intestines in the umbilical cord. Another litter had one fetus with frontal bone malformation. It is more likely that multiple rare malformations in treated litters are due to treatment than are spontaneous. The RDTS agreed that the original historical control data for the rabbit study was inappropriate. Additional historical control data provided by the sponsor was also considered inappropriate as it was from a different facility and different strain of rabbit than those involved in the EFD studies. Overall, the historical control data was not seen as supportive of the sponsor's interpretation.

The committee offered two different opinions as to the maternal no observed adverse effect level (NOAEL) for the rabbit EFD. Three RDTS members considered the maternal NOAEL to be the lowest dose tested (0.75 mg/kg), based on increased abortions with associated effects on body weight, food consumption, and clinical signs for animals that aborted. Two RDTS members considered the maternal NOAEL to be the high dose, based on the lack of maternal effects among rabbits with viable litters. That is, the committee members considered the abortions treatment-related but reproductive toxicity rather than maternal toxicity.

Reference ID: 4691893

1.3 Recommendations

It is recommended that the treatment-related embryo-fetal effects be described in the label.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional) 1350653-20-1

Generic Name vericiguat

Code Name BAY1021189, MK1242

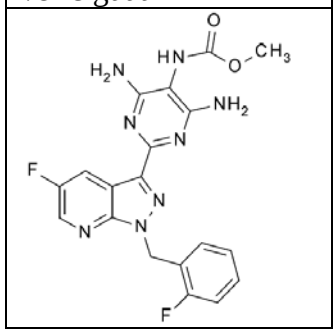
Chemical Name

Chemical name / IUPAC	Methyl {4,6-diamino-2-[5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl}carbamate
Other names	Methyl N-[4,6-diamino-2-[5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl]carbamate
	Methyl [4,6-diamino-2-[5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl]carbamate

Molecular Formula/Molecular Weight: $C_{19}H_{16}F_2N_8O_2$/ 426.39

Structure or Biochemical Description

vericiguat



Pharmacologic Class: soluble guanylate cyclase stimulator/ vasodilator

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND116743

2.7 Regulatory Background

Reference ID: 4691893

The rat and rabbit embryo-fetal development studies were interpreted by the reviewer to show signals for embryo-fetal toxicity related to treatment with vericiguat (variations in the rat study, malformations in the rabbit study). This, along with a summary of findings from other sGC stimulators that have provided Segment II reports was summarized for the NDA mid-cycle meeting and is provided as an appendix to this report. The sponsor did not agree with the reviewer's interpretation and stated that the incidence of malformations was within the historical control range and spontaneous, rather than treatment-related. The nonclinical reviewer did not consider the historical control data supportive of the sponsor's conclusion. The most relevant historical control information should be generated within 3-5 years of the conduct of the study, in the same strain of animal from the same place of origin, from the same facility in which the study was conducted. As shown in the reviewer's summary table below, the historical control data did not adequately meet this criteria. The sponsor was asked to provide additional, more relevant data on the historical incidence of these rare malformations.

Reviewer's summary of historical control data

Study/Date initiated	Species/strain	Range of historical control data (strain)	Years missing
Ttph38326/ 29 Jan 2014	Rabbit(Crl:KBL(NZW)BR)	1982 (CHBB:HM)- 2010 (CHBB:HM)	2005, 2009
Ttph38325/ 14 Nov 2012	Rat(Hsd Cpb:WU)	1987(Hsd Cpb:WU)-2009 (Hsd Cpb:WU)	2007, 2010

Sdn0023 18 September 2020

Response to first request for additional historical control data

Table 4-3: Historical Control Data for New Zealand White [Crl:KBL(NZW)BR] Rabbits: Soft Tissue Abnormalities – Persistent Trucus Arteriosus or Ventricular Septum Defect

Tissue	Abnormality		N	N	%	N	N	%
			Dose-Range Finding Studies			Full Studies		
Vessels	Persistent truncus arteriosus	L	3	0-1	(0-20.0)	11	0-1	(0-20.0)
		F	3	0-1	(0-1.7)	12	0-1	(0-1.7)
Heart	Ventricular septum defect or interventricular septal defect)	L	4	0-1	(0-20.0)	27	0-3	(0-20.0)
		F	4	0-1	(0-1.8)	29	0-3	(0-1.7)

Extracted from Charles River, Reproductive Toxicology, Historical Control Data in Rabbits. Charles River Laboratories, Pennsylvania, last updated January 2018. https://www.criver.com/sites/default/files/noindex/historical-control-data/hcd-pa-rabbits.pdf. [Ref. 4.3: 05FWVB]

F = Fetal incidence; L = Litter incidence; N = Number

Dose Range Finding Studies: No. of Studies Included = 8; No. of Litters Examined = 50; No of Fetuses Examined = 483
Full Studies: No of Studies Included = 43; No. Litters Examined = 787; No. Fetuses Examined = 7843

Sdn 0026 response to request for appropriate historical control data

COMPANY RESPONSE:

Crl:KBL(NZW)BR rabbits were used in embryofetal development study (PH-38326). In the facility conducting this study, there are no historical control data available for the Crl:KBL(NZW)BR rabbit strain. Historical control data for the CHBB:HM strain at the conducting facility is provided as an appendix in the rabbit EFD study report (PH-38326) and tabulated for cardiac ventricular septal defect between years 2008-2010 (see Table 2 below). There were no fetuses with truncus arteriosus observed in these two studies. This is the only historical control data available from the facility conducting study within the 3-5-year timeframe.

In the September 18th response, the sponsor also combined the incidence in rabbits of cardiac ventricular septal defect with the incidence of truncus arteriosus, as shown in the sponsor's table below:

Reference ID: 4691893

Table 4-1 Fetal and Litter Incidence of Truncus Arteriosus and Ventral Septal Defect (VSD), as well as Combined Incidence in the Developmental Toxicity Study in Rabbits (PH-38326)

Malformation	Cardiac ventricular septal defect, truncus arteriosus[a]	Cardiac ventricular septal defect[a]	Combined cardiac ventricular septal defect plus cardiac ventricular septal defect, truncus arteriosus[a]
Fetuses affected	0 – 0 – 2 - 1	3 – 0 – 2 – 1	3 – 0 – 4 – 2
Fetal incidence	0% – 0% - 1.6% - 1.3%	2.2% - 0% - 1.6% - 1.3%	2.2% - 0% - 3.2% - 2.6%
Litters affected	0 – 0 – 2 - 1	3 – 0 – 2 – 1	3 – 0 – 4 – 2
Litter incidence	0% – 0% - 11.8% - 10%	17.6% - 0% - 11.8% - 10%	17.6% - 0% - 23.5% - 20%

a = fetal and litter incidences for control, 0.75, 2.5 and 7.5 mg/kg/day, respectively.

A consult was then requested from CDER's Reproductive Toxicology Subcommittee (RTS). While there was also a signal in the rat EFD, the focus of the consult request was the rabbit EFD and whether the complex heart and major vessel malformation was considered treatment-related. Note: a copy of the consult is attached in its entirety as an Appendix to this review.

Reviewer's Summary of Study Reports Referenced in This Review

Report Identification	
Ttph38325	Prenatal development study in rats including toxicokinetics
Ttph38326	Prenatal development study in rabbits
T100654-6	Pilot Prenatal developmental toxicity study in rabbits (Appendix to the definitive GLP study)

4 Pharmacology

BAY1021189 is a soluble guanylate cyclase (sGC) stimulator proposed for chronic heart failure. A failing heart does not maintain the cardiac output needed to meet peripheral demands. The physiologic compensation of neurohormonal responses includes increased sympathetic nervous tone, attenuated vagal tone, renin-angiotensin-aldosterone system activation, and release of antidiuretic hormone/arginine vasopressin. The net result of these neurohormonal responses is increased vascular volume from Na+ and water retention, increased thirst and increased vascular tone. Other manifestations are vasoconstriction with increased peripheral vascular resistance, increased ventricular preload and afterload. Chronic manifestation of these compensatory mechanisms accelerates deterioration of cardiac function and promotes pathologic remodeling.

On a cellular level, the disease process disrupts signaling within the NO-sGC-cGMP pathway, leading to endothelial function disruption, hypothesized to be a predominant cause of the dysregulation of vascular tone. The pharmacological rationale for this IND is that stimulation of soluble guanylate cyclase in vascular smooth muscle will result in vasodilation, reduced vascular tone and reduced cardiac afterload, slowing the pathologic processes of heart failure.

Reference ID: 4691893

9 Reproductive and Developmental Toxicology

Cardiovascular Malformations in Rabbits

The reviewer's table below summarizes the rabbit embryo-fetal development findings from the definitive study with vericiguat.

Summary of Cardiovascular Malformations in the Rabbit Embryo-Fetal Development Study

Dose in the definitive rabbit EFD study (mg/kg)_	0	0.75	2.5	7.5
Cardiac ventricular septal defect	3 pups (3 litters)	0	2(2)	1
Malformation of heat and major vessels, cardiac septal defect, truncus arteriosus communis	0	0	2(2)	1
Right ventricle enlarged	0		1	
Total number of litters affected	3	0	4	2
Number in parentheses ( ) is number of litters affected.				

In the mid-cycle communication response, the sponsor proposed that the incidence of defects is within historical controls using published data from another facility and combining malformations of heart and great vessels.

Table from original report

Table 5-6: Fetal Malformations

Malformation	Dose (mg/kg bw/day) 0	0.75	2.5	7.5
1st sacral vertebral arch left looks like a lumbar vertebral arch; pelvis left shift to caudal	4 (4)	-	-	4 (4)
1st sacral vertebral arch right looks like a lumbar vertebral arch; pelvis right shift to caudal	1	1	1	3 (3)
great parts of frontal bones are missing	-	-	-	1
one supernumerary presacral vertebra, right arch of presacral vertebra looks like 1st sacral vertebral arch	1	-	-	-
one supernumerary presacral vertebra; pelvis left slightly shifted to cranial; left arch of presacral vertebra looks like 1st sacral vertebral arch	-	-	1	1
thickened ribs	2 (1)	1	-	-
one supernumerary presacral vertebra	27 (10)	38 (11)	24 (10)	21 (7)
isolated part of intestines in the umbilical cord	-	-	-	1
malformation of heart and major vessel(s) cardiac ventricular septal defect, truncus arteriosus communis	-	-	2 (2)	1
cardiac ventricular septal defect	3 (3)	-	2 (2)	1
kidney and ureter are missing	-	-	-	1
number of fetuses per group	134	145	126	78
number of fetuses with malformations	37	39	29	31
malformed fetuses per group (%)	27.6	26.9	23.7	39.7
number of litters per group	17	18	17	10
number of litters with malformations	13	11	13	9
malformed litters per group (%)	76.5	61.1	76.5	90.0

() number of litters affected

Table from mid-cycle response

Table 4-1 Fetal and Litter Incidence of Truncus Arteriosus and Ventral Septal Defect (VSD), as well as Combined Incidence in the Developmental Toxicity Study in Rabbits (PH-38326)

Malformation	Cardiac ventricular septal defect, truncus arteriosus[a]	Cardiac ventricular septal defect[a]	Combined cardiac ventricular septal defect plus cardiac ventricular septal defect, truncus arteriosus[a]
Fetuses affected	0 – 0 – 2 - 1	3 – 0 – 2 – 1	3 – 0 – 4 – 2
Fetal incidence	0% – 0% - 1.6% - 1.3%	2.2% - 0% - 1.6% - 1.3%	2.2% - 0% - 3.2% - 2.6%
Litters affected	0 – 0 – 2 - 1	3 – 0 – 2 – 1	3 – 0 – 4 – 2
Litter incidence	0% – 0% - 11.8% - 10%	17.6% - 0% - 11.8% - 10%	17.6% - 0% - 23.5% - 20%

a = fetal and litter incidences for control, 0.75, 2.5 and 7.5 mg/kg/day, respectively.

Reference ID: 4691893

The RTS was provided with the original review of the EFD studies and links to the sponsor's reports. Further information was requested by the RTS which included detailed descriptions of the malformations and appropriate historical controls. The specific individual animal data was provided from the study reports. The subcommittee concluded that there was no relevant historical control data. Below is an excerpt from the consult:

4.1 No relevant historical control data

- Several RDTS members discussed and had requests for clarification about the historical control data for the rabbit EFD study.
- The laboratory has no directly relevant historical control data. Bayer Healthcare was the original Sponsor for IND 116743, and conducted the rabbit EFD study at Bayer Pharma AG, Germany using New Zealand White rabbits. Their reported EFD historical control data are for the Himalayan rabbit (CHBB) (report pages 405-436). Historical control data are missing for 2005 and 2009 because the laboratory did not conduct rabbit EFD studies those years.
- Generally, P/T wants to see the study laboratory's historical control data for the 3-5 years prior to date of study conduct. All historical control data should be included, whether their target malformation was detected or not for any particular year.
- One RDTS member noted:
    - When concurrent control data are entirely out-of-range compared to typical HCD, such data should not be used to interpret study findings. This was the case with this study. In this application, the need for adequate HCD <u>in the correct strain</u> is important, given the level of rare malformations in the concurrent control group. The sponsor did not provide adequate HCD, and such data should not be the basis for sponsor conclusions.
    - On a practical level, the conclusion that these malformations are treatment-related will not change (i.e. these are rare malformations <u>in any strain</u>, and study litter incidence will inevitably exceed HCD incidence).
- Another RDTS member remarked, I would go on the assumption that Bayer submitted the historical control data they have and asking for more would seem unnecessary. However, if they wish to contest the conclusion, the appropriate historical control data as others mentioned would be a necessary component of that response and that could be communicated to them.

Another point the RTS considered was the high resorption rate in the high dose group: 28.4% versus 9.5% in the control). These were late resorptions, suggesting that many of the fetuses were not viable and subsequently were not available to be evaluated for malformations.

As also noted by the RTS, timing of exposure in a developing system is critical and the window of time in which a fetus is susceptible for a particular malformation may be very short. Cardiac malformations are associated with a high resorption rate. Few other malformations cause a nonviable embryo as the mother takes care of most essential functions in utero. Another good point brought out was that embryos implant at different times during the implantation period of gestation days (GD)4-6, meaning that each embryo in a litter is at a slightly different age with developmental windows that are slightly shifted within a litter. Given the short susceptible developmental windows, most fetuses in a litter will be refractory for a given malformation at the point when critical drug exposure levels are achieved in a fetus.

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The RTS also identified additional rare malformations. This is described in the following paragraph taken directly from the consult.

- Regarding the question of rare malformation incidence, I count a total of 4/10 high-dose litters with rare malformations (i.e. two others in addition to the VSD and TAC):
  - One litter (one fetus) with missing right kidney and ureter, and "isolated part of intestines in the umbilical cord" (female # 174, fetus # 149).
  - One litter (one fetus) with "great parts of the frontal bones are missing" (female # 151, fetus # 4)
  - The two litters with VSD were female # 159 and female # 206

The historical control data provided as part of the original EFD study in rabbits indicated that missing kidney and ureter, as well as missing portions of frontal bones are rare malformations, with fetal incidence less than 1%. It has already been stated why the historical control data does not meet criteria for optimum relevance. Different, more appropriate historical control information is needed if the sponsor wishes to interpret these particular malformations as common spontaneous findings. The presence of multiple rare malformations in the high dose group supports the conclusion that vericiguat is teratogenic.

The potential mechanism of the malformations

While there is no clearly identified mechanism of action for the malformations, the pharmacology of the drug is hypotension via stimulation of the sGC pathway. The pharmacology suggests the possibility of hypoxia or abnormal blood vessel growth. The blood pressure lowering effect of vericiguat has not been studied in rabbits but has been shown to cause vasorelaxation in isolated rabbit saphenous arteries. A generalized hypotensive effect in rabbits is expected, similar to all other species that have been studied with this drug It is unknown whether or not vericiguat produces an effect on the placental vasculature and if so, how this effect compares with the effect on the peripheral and/or cardiac vasculature and if the effect is uniform across the placenta. There was no histological or other evaluation of the whitish punctiform areas seen in three placentas of three litters in the 7.5 mg/kg/day group. The placentas of the other dose groups were similar in appearance to the control group.

There is no consistent single malformation across the drugs in the small sample of sGC stimulators/activators summarized for the mid-cycle meeting. The observations made by the RTS pertaining to different developmental ages based on time of implantation, the short developmental windows for certain malformations to occur, and the possibility of unequal pharmacological effects throughout the placenta suggest plausible explanations as to the variety of embryo-fetal effects through the drug class to date.

Responding to the Agency's mid-cycle communication, the sponsor argued that the data do not support a strong association between the expected hemodynamic effects and the observed malformation of heart and major vessels. Their rationale is that there was no treatment-related increase in VSD (with or without TA) in the rat EFD study with vericiguat despite high systemic exposures in rats associated with significant blood pressure lowering. These exposures were similar to or exceeded those seen in the rat EFD study with riociguat. The sponsor wishes to

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distinguish the embryo-fetal effects of vericiguat from riociguat, two structurally very similar drugs. Of note, treatment-related VSDs were observed in the rat EFD study with riociguat.

The sponsor also argued that malformations could be secondary to the maternal toxicities. The mid-dose and high-dose group demonstrated maternal toxicities of decreased body weight gain, decreased or no food consumption, and increased number of abortions. 3 (out of 20) females in the 2.5 mg/kg group and 8 (out of 25) females in the 7.5 mg/kg group had to be euthanized due to abortion(s) and clinical signs from day 24 p.c. onwards.

This reviewer considers the NOAEL for the maternal toxicities and intrauterine development to be 0.75 mg/kg/day, based on increased abortions with associated effects on body weight, food consumption, and clinical signs for animals that aborted. This is consistent with the opinion from three out of five RDTS members and also the sponsor as stated in their amendment to the rabbit EFD report. The fetal malformation of the heart and major vessels were observed at the same dose levels that produced maternal toxicities. There were inconsistent effects on body weight gains in the 2 females at 2.5 mg/kg and 1 female at 7.5 mg/kg that carried the fetuses with the heart and major vessel malformations. Placental weights were unaffected by treatment at dose levels up to 7.5 mg/kg/day. A treatment-related effect on the placenta can't be excluded for the high dose group due to three placentas out of three litters with several whitish punctiform areas. An association with maternal toxicities is possible, but a causal relationship cannot be established conclusively.

Safety Margins

The margins of exposure have been calculated both for total drug and drug unbound to protein.

Percent unbound in rat= 4.55%, percent unbound in humans= 2.18%, percent unbound in rabbits 3.69%

The exposure margins are calculated below.

Table 2.6.6: 18 Summary of Exposure in the Developmental Toxicity Study in Rats, Day 17 P.C. (PH-38325)

Dose	[mg/kg]	5	15	50
$AUC_{(0-24)}$	[µg·h/L]	28600	67100	240000
$AUC_{(0-24)norm}$	[kg·h/L]	5.73	4.47	4.80
C_{max}	[µg/L]	2700	5490	17700
$AUC_{(0-24)}$ unbound		1301	3053	10920
Margin compared to unbound drug		8.9X	21X	75
Margin compared to total drug		4.3X	10X	35.9X
Human AUC_{0-24} 6680µg hr/l at the MRHD (145.6 is 2.18% unbound)				

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Table 2.6.6: 20 Summary of Exposure in the Developmental Toxicity Study in Rabbits, Day 20 P.C. (PH-38326)

Dose	[mg/kg]	0.75	2.5	7.5
$AUC_{(0-24)}$	[µg·h/L]	5590	24900	105000
$AUC_{(0-24)/norm}$	[kg·h/L]	7.46	9.94	13.9
C_{max}	[µg/L]	509	2180	7590
$AUC_{(0-24)}$ unbound		121.9	542.8	2289
Margin compared to unbound drug		1.29	5.76	24.4X
Margin compared to total drug		0.84X	3.73X	15.7X
Human AUC_{0-24} 6680µg hr/l at the MRHD(145.6 is 2.18% unbound)				

Suggested labeling language

8.1 Pregnancy

Risk Summary

Based on data from animal reproduction studies, Verquvo can cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy *[see Contraindications (4.X)]*. There are no available data with Verquvo use in pregnant women. In animal reproduction studies, oral administration of vericiguat to pregnant rabbits during organogenesis, at ≥ 4 times the human exposure with the maximum recommended human dose (MRHD) of 10 mg, resulted in malformation of heart and major vessels, as well as increased number of abortions and resorptions (see Animal Data). In a pre/postnatal toxicity study, vericiguat administered orally to rats during gestation through lactation (b) (4) maternal toxicity, which resulted in decreased pup body weight gain (≥10 times the MRHD) and pup mortality (24 times the MRHD) during the preweaning period *(see Animal data)*.[i]

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

(b) (4) If a patient becomes pregnant while receiving Verquvo, healthcare providers should report Verquvo exposure by calling xxx-xxx-xxxx (b) (4)

Data

Animal Data

In an embryofetal development study in rabbits, vericiguat was administered orally to pregnant rabbits during the period of organogenesis from GD 6 to 20 at doses of 0.75, 2.50 or 7.50 mg/kg/day. An increased incidence of cardiac ventricular septal defect along with truncus arteriosus communis was observed at ≥ 2.50 mg/kg/day, which is ≥ 4 times the human exposure at the MRHD. Maternal toxicity (decreased food consumption and body weight loss), which may have resulted in late spontaneous abortions and resorptions (b) (4) noted at ≥2.50 mg/kg/day (≥4 times the human exposure at the MRHD). There was no maternal toxicity or abortions/resorptions in rabbits at an exposure approximately equivalent to the human exposure at the MRHD.[ii]

In a prenatal developmental toxicity study in rats, vericiguat was administered orally to pregnant rats during the period of organogenesis from gestation days (GD) 6 to 17 at doses of 5, 15 or 50 mg/kg/day. No developmental toxicity was observed up to the highest dose (36 times the human exposure at the MRHD, total AUC). Maternal toxicity (decreased body weight gain and food consumption) was observed at ≥15 mg/kg/day (≥10 times the human exposure at the MRHD). There was no maternal toxicity at 5 mg/kg/day (4 times the human exposure at the MRHD).

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In a pre-postnatal development study in rats, vericiguat was administered orally at doses of 7.5, 15 or 30 mg/kg/day from GD 6 through lactation day 21. Maternal toxicity (decreases in food consumption and body weight gain) was observed at all dose levels (≥6 times the human exposure at the MRHD) and resulted in decreased pup body weight gain at ≥15 mg/kg/day (≥10 times the human exposure at the MRHD) and pup mortality at 30 mg/kg/day (24 times (b)(4) the MHRD).

[^{14}C]-vericiguat was administered orally to pregnant rats at a dose of 3 mg/kg. Vericiguat-related material was transferred across the placenta, with fetal plasma concentrations of approximately 67% maternal concentrations on GD 19.

12 Appendices

Appendix 1: Slides from mid-cycle summarizing sGC embryo-fetal effects to date

There are several other sGC stimulators in stages of development. Where embryo-fetal development studies have been submitted, the results were summarized for the NDA mid-cycle meeting. The slides which summarized incidences of malformations are shown here. The slides summarizing drug exposure are omitted.

Vericiguat BAY1021189 Embryo-Fetal Development Results

RAT dose mg/kg	0	5	15	50
Litters evaluated	21	22	21	21
Thymus extended cranially	10(7)	20(14)	21(13)	37**(16*)
Incompletely ossified sternebrae 2nd	30(14)	40(14)	40(15)	53**(21)
Wavy ribs (sum)	1(1)	10*(4)	14**(6)	7(4)

( ) number of litters affected
Statistically significant difference to the control ** = p<0.01; *=p<0.05

RABBIT Dose (mg/kg)	0	0.75	2.5	7.5
Litters evaluated	17	18	17	10
cardiac ventricular septal defect , truncus arteriosus communis:litter incidence	0	0	2	1
Right ventricle enlarged, left ventricle reduced in size	0	0	1	0

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

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(b) (4)

Appendix 2. Pharmacology/Toxicology Reproductive and Developmental Toxicology Subcommittee Consult Response

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U.S. FOOD & DRUG ADMINISTRATION

PTCC Reproductive and Developmental Toxicology Subcommittee (RDTS) Consult Response

DATE: 10/13/2020

TO: Elizabeth Hausner, DVM, Division of Cardiology and Nephrology (DCN)

FROM: David Klein, RDTS Secretary; Sushanta Chakder, RDTS Chair; and Andrew McDougal, RDTS Co-Chair, on behalf of RDTS

SUBJECT: Vericiguat (IND 116743 / NDA 214377)

COMMITTEE MEMBERS:

Sushanta Chakder, Andrew McDougal, David Klein, Karen Davis Bruno, Tessie Alapatt, Ilona Bebenek, Kelly Brant, Pedro DelValle, Aling Dong, Amy Ellis, Darren Fegley, Edward Fisher, Wafa Harrouk, Kimberly Hatfield, Carlic Huynh, Lori Kotch, Gracee Lee, Steve Leshin, Dan Minck, Mukesh Summan, Amy Nostrandt, Sonia Tabacova, Baichun Yang, Ita Yuen, Eias Zahalka

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The consult was received September 24, 2020. Since the next RDTS committee meeting would have fallen on a federal holiday (October 12, 2020), the consult was discussed via email.

1 Questions to the Subcommittee

Does the RDTS consider the incidence of malformation of the heart and great vessels to be related to drug treatment?

- Riociguat, the first soluble guanylate cyclase stimulator that DCRP approved, was labelled for causing embryo-fetal defects (cardiac). Vericiguat is now in the NDA stage and structurally similar to riociguat. Vericiguat also seems to cause cardiac defects (primary reviewer interpretation) in the rabbit EFD study. The Applicant disagrees and proposes that the observations are within historical controls.
- What is the opinion of the Reproductive Toxicology committee as far as the potential of vericiguat to cause embryo-fetal defects? Is it plausible that 3 drug-treated litters affected by malformation of the heart and great vessels, historically a rare event, is unrelated to the test article?

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1.1 Primary Reviewer's Conclusions (for RDTS Concurrence)

There is an increased incidence of cardiac and great vessel malformation associated with vericiguat administration in rabbits.

2 Background and Relevant Data

- **IND116743/NDA214377**
- **Drug Name:** vericiguat
- **Division:** DCN
- **Reviewer:** Elizabeth Hausner
- **Supervisor:** Xuan Chi
- **Sponsor:** Merck/Bayer
- **Clinical Indications**: heart failure with (b) (4) reduced ejection fraction
- **Pharmacological Classification / Mechanism of Action**: soluble guanylate cyclase stimulator. This causes smooth muscle relaxation and vasodilation, reducing blood pressure and afterload on the heart
- **Brief background** :

  Riociguat, the first soluble guanylate cyclase stimulator approved by the Division of Cardiovascular and Renal Products, was labelled as causing embryo-fetal defects (cardiac). The subject of this consult is structurally similar to riociguat. The structures are provided in the attachment. There is an increased incidence of malformations of the heart and great vessels that appears only in the mid- and high-dose drug-treated groups and not in the control group. This defect is described in only 3 pups (3 different litters) in 6 years of historical controls. The sponsor has combined the incidence of ventricular septal defect (vsd) with the incidence of this malformation to say that there is no embryo-fetal effect and to distinguish vericiguat from riociguat.

2.1 Supporting Summary Information

Vericiguat (BAY1021189) is a soluble guanylate cyclase (sGC) stimulator, indicated for heart failure with (b) (4) reduced ejection fraction. The first sGC stimulator, riociguat, was approved for pulmonary arterial hypertension and is labelled as causing embryo-fetal defects (cardiac). Vericiguat and riociguat are structurally similar.

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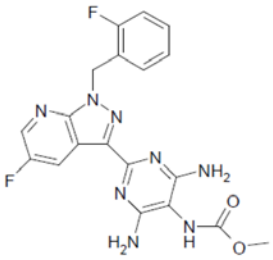
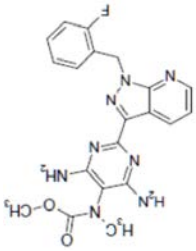
vericiguat	riociguat
	

Summary of cardiac defects in vericiguat embryo-fetal development study. Four different litters are represented in the 2.5 mg/kg group. Two different litters are represented at 7.5mg/kg for a total of 6 different drug-treated litters affected.

rabbit Dose mg/kg	0	0.75	2.5	7.5
Cardiac ventricular septal defect	3pups(3litters)	0	2(2)	1
Malformation of heart and major vessels, cardiac septal defect, truncus arteriosus communis	0	0	2(2)	1
Right ventricle enlarged			1	
Number in parentheses () is number of litters affected				

In the mid-cycle response, the sponsor contends that the incidence of defects are within historical controls using published data from another facility and combining the VSD and malformations of heart and great vessels. Study report table shown first, then the new presentation in response to mid-cycle comments.

Table from original study report	Table from mid-cycle response

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Table 5-6: Fetal Malformations

Malformation	Dose (mg/kg bw/day) 0	0.75	2.5	7.5
1st sacral vertebral arch left looks like a lumbar vertebral arch; pelvis left shift to caudal	4 (4)	-	-	4 (4)
1st sacral vertebral arch right looks like a lumbar vertebral arch; pelvis right shift to caudal	1	1	1	3 (3)
great parts of frontal bones are missing	-	-	-	1
one supernumerary presacral vertebra, right arch of presacral vertebra looks like 1st sacral vertebral arch	1	-	-	-
one supernumerary presacral vertebra; pelvis left slightly shifted to cranial; left arch of presacral vertebra looks like 1st sacral vertebral arch	-	-	1	1
thickened ribs	2 (1)	1	-	-
one supernumerary presacral vertebra	27 (10)	38 (11)	24 (10)	21 (7)
isolated part of intestines in the umbilical cord	-	-	-	1
malformation of heart and major vessel(s)	-	-	2 (2)	1
cardiac ventricular septal defect, truncus arteriosus communis				
cardiac ventricular septal defect	3 (3)	-	2 (2)	1
kidney and ureter are missing	-	-	-	1
number of fetuses per group	134	145	126	78
number of fetuses with malformations	37	39	29	31
malformed fetuses per group (%)	27.6	26.9	23.7	39.7
number of litters per group	17	18	17	10
number of litters with malformations	13	11	13	9
malformed litters per group (%)	76.5	61.1	76.5	90.0

() number of litters affected

Table 4-1 Fetal and Litter Incidence of Truncus Arteriosus and Ventral Septal Defect (VSD), as well as Combined Incidence in the Developmental Toxicity Study in Rabbits (PH-38326)

Malformation	Cardiac ventricular septal defect, truncus arteriosus[a]	Cardiac ventricular septal defect[a]	Combined cardiac ventricular septal defect plus cardiac ventricular septal defect, truncus arteriosus[a]
Fetuses affected	0 – 0 – 2 - 1	3 – 0 – 2 – 1	3 – 0 – 4 – 2
Fetal incidence	0% – 0% - 1.6% - 1.3%	2.2% - 0% - 1.6% - 1.3%	2.2% - 0% - 3.2% - 2.6%
Litters affected	0 – 0 – 2 - 1	3 – 0 – 2 – 1	3 – 0 – 4 – 2
Litter incidence	0% – 0% - 11.8% - 10%	17.6% - 0% - 11.8% - 10%	17.6% - 0% - 23.5% - 20%

a = fetal and litter incidences for control, 0.75, 2.5 and 7.5 mg/kg/day, respectively.

3 Subcommittee Consult Recommendations

- Eight RDTS members concluded that vericiguat induced malformations in the rabbit EFD study at 2.5 and 7.5 mg/kg, based on truncus arteriosus communis (TAC) at 2.5 and 7.5 mg/kg, and right ventricle enlarged/left ventricle reduced in size at 2.5 mg/kg. No RDTS members disagreed with this conclusion.

- Seven RDTS member did not consider the incidence of cardiac ventral septal defect (VSD) to be clearly treatment-related, based on the litter incidence in the concurrent control group.

- Two RDTS members did consider the incidence of VSD to be treatment-related, in context (i.e. smaller number of litters at the high-dose, and the presence of VSD and other cardiovascular abnormalities)

3.1 Points for the DPT review division to consider

- Identification of the maternal NOAEL and LOAEL for the rabbit EFD study may be important for labeling:
    - Three RDTS members considered the maternal NOAEL to be the low-dose (0.75 mg/kg), based on increased abortions with associated effects on body weight, food consumption, and clinical signs for animals that aborted.
    - Two RDTS members considered the maternal NOAEL to be the high-dose, based on the lack of maternal effects among rabbits with viable litters (i.e. considering the abortions treatment-related but reproductive toxicity rather than maternal toxicity)

- The rabbit pilot EFD study (T100654- 6) is mentioned in the GLP EFD rabbit study report (page 761).
    - 2/3 aborted at 10 mg/kg. The one remaining litter had “one fetus with common origin of innominate artery and left carotid artery at visceral evaluation”
    - Generally, these findings would not be labeled (i.e. the summary for the GLP EFD study can be written to cover these findings). However, noting them may help explain the Division’s conclusions to the Sponsor.
- For the GLP rabbit EFD study, rare malformations were observed in 4/10 litters. In addition to the cardiac malformations discussed above, one litter had a fetus with missing kidney and ureter, and isolated part of intestines in the umbilical cord. Another litter had one fetus with frontal bone malformation.
    - RDTS did not discuss these malformations or their relation to treatment in detail.
    - In considering whether a rare malformation is incidental or treatment-related, it is proportionately more likely that multiple rare malformations in treated litters are due to treatment.

4 Subcommittee Responses

4.1 No relevant historical control data

- Several RDTS members discussed and had requests for clarification about the historical control data for the rabbit EFD study.
- The laboratory has no directly relevant historical control data. Bayer Healthcare was the original Sponsor for IND 116743, and conducted the rabbit EFD study at Bayer Pharma AG, Germany using New Zealand White rabbits. Their reported EFD historical control data are for the Himalayan rabbit (CHBB) (report pages 405-436). Historical control data are missing for 2005 and 2009 because the laboratory did not conduct rabbit EFD studies those years.
- Generally, P/T wants to see the study laboratory’s historical control data for the 3-5 years prior to date of study conduct. All historical control data should be included, whether their target malformation was detected or not for any particular year.
- One RDTS member noted:
    - When concurrent control data are entirely out-of-range compared to typical HCD, such data should not be used to interpret study findings. This was the case with this study. In this application, the

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need for adequate HCD in the correct strain is important, given the level of rare malformations in the concurrent control group. The sponsor did not provide adequate HCD, and such data should not be the basis for sponsor conclusions.
  - On a practical level, the conclusion that these malformations are treatment-related will not change (i.e. these are rare malformations in any strain, and study litter incidence will inevitably exceed HCD incidence).
- Another RDTS member remarked, I would go on the assumption that Bayer submitted the historical control data they have and asking for more would seem unnecessary. However, if they wish to contest the conclusion, the appropriate historical control data as others mentioned would be a necessary component of that response and that could be communicated to them.

4.2 Data clarification

- Certain defects hang together (secondary to hemodynamic changes caused by primary malformation) and you may have a stronger case for treatment-relatedness if those relationships are known.
  - Were VSDs all isolated effects? If not, what other cardiovascular effects were found in these fetuses?

    VSD occurred in isolation (the pups listed on the first line) and in combination with other defects

  - There are 2 litters/1 fetus each with these malformations. As such, it would seem that the fetuses must have had multiple defects (since 4 are listed). Can you describe the full set of cardiovascular findings for each affected fetus?

    This is all the detail that was provided

  - Right ventricle enlarged" – did this occur in isolation? Please describe full set of cardiovascular findings for the fetus if not.

    No other findings were described in the report

  - Can you do the same for 3 control fetuses?

    No other findings were described

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- These are from the individual listings in the appendices of the report. There were no reported findings in the lowest dose group of 0.75mg/kg.

APPEARS THIS WAY ON ORIGINAL

(MAIN GROUPS)

INDIVIDUAL FETAL VISCERAL OBSERVATIONS

0 MG/KG

FEMALE#	FETUS#	ORGAN	OBSERVATION
177	167	BLOOD VESSELS	INNOMINATE ARTERY ENLARGED; LEFT CAROTID ARTERY SMALLER THAN NORMAL
	170H	HEART	CARDIAC VENTRICULAR SEPTAL DEFECT
200	320H	HEART	CARDIAC VENTRICULAR SEPTAL DEFECT
204	347	HEART	CARDIAC VENTRICULAR SEPTAL DEFECT

[0.75 mg/kg: No individual fetal visceral observations]

2.5 MG/KG

FEMALE#	FETUS#	ORGAN	OBSERVATION
160	59H	HEART	RIGHT VENTRICLE ENLARGED; LEFT VENTRICLE REDUCED IN SIZE
	60	HEART	MALFORMATION OF HEART AND MAJOR VESSEL(S) CARDIAC VENTRICULAR SEPTAL DEFECT, TRUNCUS ARTERIOSUS COMMUNIS
166	97	HEART	MALFORMATION OF HEART AND MAJOR VESSEL(S) CARDIAC VENTRICULAR SEPTAL DEFECT, TRUNCUS ARTERIOSUS COMMUNIS
176	163H	HEART	CARDIAC VENTRICULAR SEPTAL DEFECT
221	447	HEART	CARDIAC VENTRICULAR SEPTAL DEFECT

7.5 MG/KG

FEMALE#	FETUS#	ORGAN	OBSERVATION
159	52H	HEART	MALFORMATION OF HEART AND MAJOR VESSEL(S) CARDIAC VENTRICULAR SEPTAL DEFECT, TRUNCUS ARTERIOSUS COMMUNIS
174	149	KIDNEY	KIDNEY AND URETER ARE MISSING; RIGHT
189	258	LIVER	WHITISH DISCOLORATION AT THE CAUDAL END OF RIGHT UPPER LIVER LOBE 0.05 CM x 0.1 CM
206	358	HEART	CARDIAC VENTRICULAR SEPTAL DEFECT

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4.2 Collated comments & discussion regarding the fetal anomaly data (chronologic order)

- The control incidence within the study shows 3 liters with cardiac septal defects and the 2.5 mg/kg group shows 2 litters effected. The 7.5 mg/kg dose shows 1 litter effected. This doesn't appear drug related

rabbit Dose mg/kg	0	0.75	2.5	7.5
Cardiac ventricular septal defect	3pups(3litters)	0	2(2)	1
Malformation of heart and major vessels, cardiac septal defect, truncus arteriosus communis	0	0	2(2)	1
Right ventricle enlarged			1	
Number in parentheses () is number of litters affected				

- For the cardiac ventral septal defect, there is no need to compare with historical controls in this case; the concurrent control has higher incidences of cardiac ventricular septal defect than the mid dose (2/2 at 2.5 mg/kg) and there is only one incidence at the high dose of 7.5 mg/kg.

- Isn't the reviewer's primary concern about cardiac malformations that are rarely observed in the historical control database?
    - I thought Dr. Hausner was concerned that the Sponsor was combining ventricular septal defects (which are perhaps more prevalent in control animals) with the rarer cardiac/great vessel malformations thereby making the overall incidence of cardiac effects appear more similar between groups.
    - I wanted to express concern that the primary concern brought up by the reviewer consulting the RDTS should be adequately considered and addressed.

- That was also my impression, that the concern was for the more serious and rare cardiac defects, particularly truncus arteriosus communis, seen only in the treated groups. This was not a great study; for example, they are calling common skeletal variations, like supernumerary presacral vertebra, malformations.

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- Regarding the incidence of persistent truncus arteriosus only at the mid-dose and high-dose, one Subcommittee member provided a link to Developmental and Reproductive Toxicology A Practical Approach (2016, edited by Ronald Hood). [Full access is available online.]
    - I think this is what we're talking about, a similar low incidence of persistent truncus arteriosus only at the MD and HD. Pages 287-289 of this book (http://www.crcnetbase.com/isbn/9781841847771) contains a discussion of the variability in the background incidence of this defect in NZW rabbits. But because of the distribution here, I don't think a treatment effect can be ruled out. VSD usually accompanies persistent truncus arteriosus.

HEART

MALFORMATION OF HEART AND MAJOR VESSEL(S)
CARDIAC VENTRICULAR SEPTAL DEFECT, TRUNCUS ARTERIOSUS COMMUNIS

Fetal Incidence	N	0 f	0	2	1
	%	0.0	0.0	1.6	1.3
	p-value	0.241			
Litter Incidence	N	0 f	0	2	1
	%	0.0	0.0	11.8	10.0
	p-value	0.248			
Affected Fetuses/Litter	MEAN%	0.00 k	0.00	1.32	1.43
	S.D.	0.000	0.000	3.762	4.518
	p-value	0.257			

- I agree. Although the overall VSD incidence (3, 0, 4, 2) is similar between the MD, HD and C groups, the increased incidence (0, 0, 2, 1) of truncus arteriosus communis (TAC) at the MD/HD cannot be ruled out as a treatment-related effect. The MD and HD were also associated with maternal toxicity based on the increased abortions with associated effects on body weight, food consumption, and clinical signs in affected animals. To answer Dr. Elizabeth Hausner's question directly, my opinion is that there is an increased incidence of TAC at the MD/HD that occurred at doses associated with maternal toxicity

- I agree
    - persistent truncus arteriosus is a rare cardiovascular malformation and should be considered treatment-related finding based on the presence of the malformation at doses ≥2.5 mg/kg.
    - Given the missing historical control data, it is difficult to get a confident litter incidence. The Charles River Lab HCD (2011-2019) supports that persistent truncus arteriosus is a rare malformation. The % litter incidence of persistent truncus arteriosus is 0.63% and 0.3% for 2011-2013 and 2014-2019, respectively. Although not the conducting labs

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HCD, the Charles River data can provide some general information regarding species incidence.
  - The %litter incidence for VSDs in Sponsors study, and their HCD, were 7.5% and 6%, respectively, while Charles River Lab HCD was 1.1%. I am not sure how to explain the difference (…they ought to consider a different vendor with that kind of background rate).
  - For the purpose of utilizing HCD, isolated effect should be compared. The practice of grouping effects alters this comparative assessment and is not acceptable.
  - Rare malformation such as those in this study (persistent truncus arteriosus, vsd) should be highlighted in the label.

- I agree that TAC malformations are treatment related. I also think VSDs and 'enlarged right ventricle/small left ventricle' are treatment related. The HCD sent by the sponsor are not adequate.
  - Given the # of total resorptions/abortions at the high dose, # of viable litters is reduced in this group (1/2 that of other groups). As such, litter incidence for cardiac effects were ~same across mid and high dose groups for cardiac malformations.
  - Based on individual visceral exams (see below) all truncus arteriosus communis (TAC) in mid and high dose was associated with VSD. In addition, there were three isolated VSD in the mid and high dose groups. As such, VSD occurred in 6 fetuses in mid and high groups, compared to 3 in control.
  - Given the other treatment-related cardiovascular effects, enlarged right ventricle (with accompanying small left ventricle) in mid-dose should not be dismissed. This effect should be considered treatment-related.
  - The sponsor proposes to dismiss (rare) malformations on the basis they occur in a single fetus/litter or do not occur in a dose dependent manner. This approach toward interpretation of DART data is unacceptable. Keep in mind that current policy, as set forth in guidance, emphasizes the point that one cannot expect dose-dependency for rare events, as discussed in the 2011 Guidance for Industry Reproductive and Developmental Toxicities — Integrating Study Results to Assess Concerns and ICHS5(R3).
  - As mentioned, lab's background rate for cardiac effects is high, however the HCD data provided appears to be incomplete (missing two years), which may contribute to the high litter incidences. That such data is entirely inconsistent with other large HC datasets (Charles River Labs, as Eias mentions), further elevates concern regarding the conducting lab's HCD. It is not appropriate to use the HCD of other labs, so it would be better to try and get the full HCD for the conducting lab from the sponsor.

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APPEARS THIS WAY ON ORIGINAL

(RATH GROUPS)
INDIVIDUAL FETAL VISCERAL OBSERVATIONS

0 MG/KG

FEMALE#	FETUS#	ORGAN	OBSERVATION
177	167	BLOOD VESSELS	INNOMINATE ARTERY ENLARGED; LEFT CAROTID ARTERY SMALLER THAN NORMAL
	170H	HEART	CARDIAC VENTRICULAR SEPTAL DEFECT
200	320H	HEART	CARDIAC VENTRICULAR SEPTAL DEFECT
204	347	HEART	CARDIAC VENTRICULAR SEPTAL DEFECT

2.5 MG/KG

FEMALE#	FETUS#	ORGAN	OBSERVATION
160	59H	HEART	RIGHT VENTRICLE ENLARGED; LEFT VENTRICLE REDUCED IN SIZE
	60	HEART	MALFORMATION OF HEART AND MAJOR VESSEL(S) CARDIAC VENTRICULAR SEPTAL DEFECT, TRUNCUS ARTERIOSUS COMMUNIS
166	97	HEART	MALFORMATION OF HEART AND MAJOR VESSEL(S) CARDIAC VENTRICULAR SEPTAL DEFECT, TRUNCUS ARTERIOSUS COMMUNIS
176	163H	HEART	CARDIAC VENTRICULAR SEPTAL DEFECT
221	447	HEART	CARDIAC VENTRICULAR SEPTAL DEFECT

7.5 MG/KG

FEMALE#	FETUS#	ORGAN	OBSERVATION
159	52H	HEART	MALFORMATION OF HEART AND MAJOR VESSEL(S) CARDIAC VENTRICULAR SEPTAL DEFECT, TRUNCUS ARTERIOSUS COMMUNIS
174	149	KIDNEY	KIDNEY AND URETER ARE MISSING; RIGHT
189	258	LIVER	WHITISH DISCOLORATION AT THE CAUDAL END OF RIGHT UPPER LIVER LOBE 0.05 CM x 0.1 CM
206	358	HEART	CARDIAC VENTRICULAR SEPTAL DEFECT

- I also concur that vericiguat exposure is associated with malformations of the great vessels of the heart. The rabbit pilot EFD study provides some additional support
  - a short summary of the pilot rabbit EFD study (T100654- 6) is included in the GLP rabbit embryofetal development toxicity study (report # PH-38326, page 761)
  - Groups of 3 mated female NZW rabbits: 0, 1, 3, or 10 gm/kg/day
  - Reduced weight gain reported for 3 and 10 mg/kg
  - 2/3 aborted at 10 mg/kg. The one remaining litter had “one fetus with common origin of innominate artery and left carotid artery at visceral evaluation”

- I also agree that TAC malformations are vericiguat-related in this study and comparing an appropriate HCD from the same strain and the recent timeframe (the last five years or longer from conducting the study) is important. I also agree that dose-dependency cannot be expected for rare malformations. In addition, in this study, there was a high resorption rate in the high dose group (28.4% vs. 9.5% in the control) and if I read it correctly,

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these were all late resorptions. In my opinion, this is another reason that we cannot expect dose-dependency for vericiguat-related findings as many affected fetuses in the high dose group were not likely viable and subsequently were not able to evaluate for any abnormalities.

- For rare malformations, how much is known if they are rare because the animals do not survive to the day of necropsy, and may actually be “more” common, or do they survive and the rare incidence is a true reflection of incidences. Any insight available or example of known rare malformations?
    - Response 1: The time of exposure related to the developing system is crucial for causing embryo-fetal abnormalities. Perhaps, the critical window to inducing a rare (very specific) malformation might be short and the embryos need to be exposed to the substantial amount of the drug at the right time of the development in order to induce that specific malformation. In my opinion, this might be one of the factors for rare malformations.
    - Response 2: this answer is correct, on all fronts.
        - Cardiac malformations are often associated with high resorption rate. Few other malformations can kill an embryo or fetus (e.g. fetuses live with complete absence of brain tissue, limbs, gastroschisis, massive facial clefts; mother takes care of most essential functions in utero). As such, Grace makes a good point that level of death at high dose likely precludes determination of dose dependency for these particular cardiac malformations.
        - Across the board, rare malformations are rare (incidence <1%) because critical developmental windows during which they can be produced are short, and embryo is refractory for that same malformation after that.
        - Given embryos implant at different times over the course of two days (GD 4-6 in rodents), each embryo in a litter is at a slightly different age. This means that developmental windows across embryos within a litter are slightly shifted.
        - Given the short critical developmental windows, most embryos within a litter will be refractory for a particular malformation, at the point when critical drug exposure levels are achieved in an embryo. You would be lucky if you hit just a couple of embryos with the drug per study; affected embryos may or may not be in the same dose group.
        - Conversely, malformations with long critical developmental windows (e.g. skeletal malformations) will not be rare, and dose dependency can be expected. You have to use the HCD to understand the difference between a rare vs. frequent malformation.

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- Regarding the question of rare malformation incidence, I count a total of 4/10 high-dose litters with rare malformations (i.e. two others in addition to the VSD and TAC):
  - One litter (one fetus) with missing right kidney and ureter, and "isolated part of intestines in the umbilical cord" (female # 174, fetus # 149).
  - One litter (one fetus) with "great parts of the frontal bones are missing" (female # 151, fetus # 4)
  - The two litters with VSD were female # 159 and female # 206
- For the control group, 3/17 litters have VSD, and I don't see other malformations.
- For the 2.5 mg/kg group, 4 litters were affected (one litter with two affected fetuses). Nothing identified beyond what is shown in the Individual Fetal Visceral Observation tables captured above.

- The mechanism of action of vericiguat is hypotensive via sGC activation. The high-dose had 3 placentae with "several whitish punctiform areas". The authors considered the effect treatment-related but not adverse. Is it a concerning observation? I'm wondering whether it suggests toxicity due to primary pharmacology (e.g. hypoxia or abnormal blood vessel growth).

7.5 MG/KG

FEMALE#	FETUS#	ORGAN	OBSERVATION
151	4	PLACENTA	SEVERAL WITISH PUNCTIFORM AREAS
168	106	PLACENTA	SEVERAL WITISH PUNCTIFORM AREAS
	111	PLACENTA	PARTS OF PLACENTA HARDENED AND LIGHT DISCOLORED
183	212	PLACENTA	PARTS OF PLACENTA HARDENED AND DARK DISCOLORED
	218	PLACENTA	SEVERAL WITISH PUNCTIFORM AREAS

- Response 1: There was yellowish placenta discoloration along the edges in the mouse study as well. Could it be the drug or its metabolites? Without histology it is difficult to determine if it is represents an infectious process.
- Response 2: Referencing the book mentioned above (Developmental and Reproductive Toxicology A Practical Approach, 2016, edited by Ronald Hood), I also noticed a section on rabbit gall bladder absence, p. 265.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA214377
Supporting document/s:	0024
Applicant's letter date:	September 25, 2020
Product:	Vericiguat BAY1021189
Indication:	Heart failure
Applicant:	Merck
Review Division:	DPT for OCHEN
Reviewer:	E.A. Hausner
Supervisor/Team Leader:	Xuan Chi
Division Director:	Todd Bourcier
Project Manager:	Alexis Childers

Template Version: September 1, 2010 (Modified by DCRP: June 10, 2013)

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Any information or data necessary for approval of [NDA number] that [name of applicant] does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of [NDA number].

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13 APPENDIX/ATTACHMENTS..... ERROR! BOOKMARK NOT DEFINED.

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1 Executive Summary

1.1 Introduction (and Clinical Rationale)

Vericiguat is a soluble guanylate cyclase stimulator developed for chronic heart failure. Soluble guanylate cyclase stimulates production of cGMP, a signaling molecule that is involved in vascular smooth muscle relaxation, cardiac contractility, and cardiac remodeling. It is proposed that vericiguat can help remediate deficiencies in intracellular cGMP levels thus improving myocardial and vascular function via vasodilation and decreasing cardiac afterload.

1.2 Brief Discussion of Nonclinical Findings

Vericiguat and BAY10222707 (M1 metabolite) were evaluated for possible interaction with the several cardiac ion channels including hERG, hNav1.5, hCav1.2, hKvLQT1, and hKv4.3. The protocols reported deviate from the recommended Comprehensive in vitro Proarrhythmia Assay (CIPA) assays in several respects. The sponsor used internal and external solutions of different composition than recommended, different voltage protocols, and did not conduct or did not provide analysis of the outflow solutions for verification of concentration. The voltage protocol used for the sodium channels will not capture effects on the late Na+ channel. Determination of baseline stability for each ion channel was also discussed in general terms rather than providing the detailed method recommended for each ion channel. (b) (4) The temperature at which the experiment is conducted may affect the magnitude of the ion channel current, the configuration of the channel, as well as the concentration of drug needed to produce a detectable effect(Kirsch et. al. J Toxicol. Pharmacol. Methods, 2004). Validation of the temperature used for this platform was not provided.

Another possible deviation was the frequencies at which data were filtered and digitized. These values were not reported. The positive controls used were different than those recommended under CIPA. The different reports state that adequate seal pressure was reached, but means of determination (e.g. baseline) was not noted.

The medical officers also requested that the conditions used mimic worst case scenarios in the patient population. The reported stimulation frequencies were (b) (4). A stimulation frequency of 3 Hz simulates the upper range of human heart rate according to the sponsor's own reference (Harmer et. al. J. Pharmacol. Toxicol. Methods, 2008). This is a frequency which will also distinguish compounds that show a use-dependent block, chemicals that may not appear as potent at lower stimulation rates.

A final point of concern is the purity of the material used for the M1 assays. The certificate of analysis states that the material was demonstrated to have (b) (4)% purity. This is unacceptably low as the (b) (4)% of unknown material may itself interfere with detection of ion channel effects, e.g. physical or pharmacological block of a channel.

Despite these assay limitations, vericiguat showed an IC_{50} for hERG of approximately 4µM, still in the same order of magnitude as the original hERG assay and the IC_{50} of 10µM.

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The clinical Cmax of vericiguat for 10 mg per day in healthy volunteers is 398µg/L. The molecular weight of vericiguat is 426.39 g/mole. The human Cmax is therefore 0.9µM for total drug. There is an apparent safety margin of (b) (4) between the Cmax and the IC_{50} value for hERG interaction. The ECTD Clinical Pharmacology summary states the steady state Cmax in the combined Phase2 and 3 population as 350µg/L or 0.8µM. When free drug is considered, (7.7ng/ml) the margin of safety is (b) (4). However, given the unreliability of the assay results, these ratios and apparent safety margins do not necessarily reflect reality.

1.3 Recommendations

The sponsor did not provide validation for the methods used. The (b) (4) was suboptimal and the purity of the M1 test material was unacceptable. Despite this, there appears to be some interaction of the parent drug with the hERG channel. Given this and the relatively low apparent margin of safety, it seems reasonable to repeat these assays using validated methods and test material of acceptable purity.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional) 1350653-20-1

Generic Name vericiguat

Code Name BAY1021189, MK1242

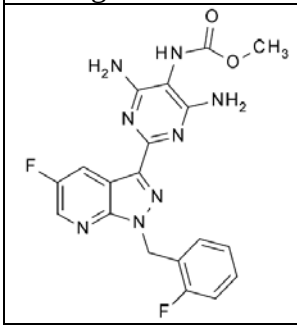
Chemical Name

Chemical name / IUPAC	Methyl {4,6-diamino-2-[5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl}carbamate
Other names	Methyl N-[4,6-diamino-2-[5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl]carbamate
	Methyl [4,6-diamino-2-[5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl]carbamate

Molecular Formula/Molecular Weight $C_{19}H_{16}F_2N_8O_2$/ 426.39

Reference ID: 4683123

Structure or Biochemical Description

vericiguat


Pharmacologic Class soluble guanylate cyclase stimulator/ vasodilator

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND116743

2.7 Regulatory Background

This amendment was prompted by an increased incidence of sudden death in patients without implanted cardiac defibrillators (“pacemakers”). The Medical Officer considered this to be possibly associated with pro-arrhythmic events. In an effort to find mechanistic support for this consideration, the sponsor was asked to investigate the interaction of the parent drug, vericiguat, and the M1 metabolite with the cardiac ion channels. The expectation was that this would be conducted by the guidelines in the Comprehensive in vitro Proarrhythmia Assay (CIPA) protocols and would include voltage courses to simulate worst case scenarios. Details of the electrophysiology were discussed with Victor Long, Ph. D. , who has expertise in this area.

4 Pharmacology

BAY1021189 is a soluble guanylate cyclase (sGC) stimulator proposed for chronic heart failure. A failing heart does not maintain the cardiac output needed to meet peripheral demands. The physiologic compensation of neurohormonal responses includes increased sympathetic nervous tone, attenuated vagal tone, renin-angiotensin-aldosterone system activation, and release of antidiuretic hormone/arginine vasopressin. The net result of these neurohormonal responses is increased vascular volume from Na+ and water retention, increased thirst and increased vascular tone. Other manifestations are vasoconstriction with increased peripheral vascular resistance,

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increased ventricular preload and afterload. Chronic manifestation of these compensatory mechanisms accelerates deterioration of cardiac function and promotes pathologic remodeling.

On a cellular level, the disease process disrupts signaling within the NO-sGC-cGMP pathway, leading to endothelial function disruption, hypothesized to be a predominant cause of the dysregulation of vascular tone. The pharmacological rationale for this IND is that stimulation of soluble guanylate cyclase in vascular smooth muscle will result in vasodilation, reduced vascular tone and reduced cardiac afterload, slowing the pathologic processes of heart failure.

4.3 Safety Pharmacology

Original hERG Study (submitted with IND opening material)

(b) (4)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA214377
Supporting document/s:	0001
Applicant's letter date:	May 20, 2020
CDER stamp date:	May 20, 2020
Product:	Vericiguat (BAY1021189)
Indication:	Chronic heart failure
Applicant:	Merck
Review Division:	DPT for OCHEN
Reviewer:	E.A. Hausner
Supervisor/Team Leader:	Xuan Chi
Division Director:	Todd Bourcier
Project Manager:	Alexis Childers

Template Version: September 1, 2010 (Modified by DCRP: June 10, 2013)

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1 Executive Summary

1.1 Introduction (and Clinical Rationale)

Vericiguat is a soluble guanylate cyclase (sGC) stimulator developed for chronic heart failure. Soluble guanylate cyclase stimulates production of cGMP, a signaling molecule that is involved in vascular smooth muscle relaxation, cardiac contractility, and cardiac remodeling. Both the NO-sGC-cGMP and natriuretic peptide-particulate guanylate cyclase-cGMP signaling pathways are important for vasorelaxation and myocardial function. An insufficiency of NO can lead to problems with endothelium-dependent vascular tone. It is proposed that vericiguat can help remediate deficiencies in intracellular cGMP levels and thus NO signaling pathways, improving myocardial and vascular function via vasodilation and decreasing cardiac afterload.

1.2 Brief Discussion of Nonclinical Findings

The sponsor has conducted nonclinical studies in vitro and in vivo to characterize the pharmacological properties of BAY1021189. In addition, in vitro activity of the major circulating metabolite in human (M-1; N-glucuronide of vericiguat) was also determined. Potential off-target pharmacology was assessed in receptor binding and enzyme interaction studies. In vitro and in vivo safety pharmacology studies were conducted according to ICHS7A and S7B guidelines.

Nonclinical studies of the absorption, distribution, metabolism, and excretion were evaluated in addition to the nonclinical toxicology studies recommended under the ICH guidelines to support chronic use of vericiguat in humans. The portfolio of toxicology includes repeat dose toxicology studies up to 6 months duration in rats, up to 39 weeks in dogs, 2-year rodent carcinogenicity studies, a standard battery of genetic toxicology assays, developmental and reproductive toxicology and juvenile animal studies. The pivotal studies were conducted in accordance with GLP guidelines and used the oral route of administration, consistent with the clinical route of administration. There are no novel excipients and all excipients in the drug product are within the IID levels with respect to maximum daily intake. There are no drug substance or drug product impurity issues.

The primary pharmacology of vericiguat is smooth muscle relaxation by stimulating sGC and increasing intracellular cGMP levels. This produces vasodilation, reduced vascular tone, and reduced cardiac afterload. Systolic, diastolic, and mean arterial blood pressure are consistently lowered, with concomitantly increased heart rate.

Other effects associated with the pharmacology include altered gastrointestinal motility and bone metabolism. The reduced gastrointestinal motility in rats was mediated by relaxation of smooth muscle cells and observed at 6-fold the therapeutically effective human plasma Cmax. The bone effects were most apparent in the shorter-term studies using adolescent rats and included hypertrophy of the growth plate, hyperostosis, and remodeling of metaphyseal and diaphyseal bone. Effects were noted in a juvenile rat pilot study when the pups were administered an amount of vericiguat exceeding a maximally tolerated dose. Bone effects were not obvious in the 2-year carcinogenicity studies in rats and mice. Bone effects were not reported for the repeat

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dose toxicology studies in dogs or the 6-month toxicity study in rats. However, in the 13-week repeat dose toxicity study in rats, bone hyperostosis and remodeling were observed at 30 mg/kg. Of note, the animal age at the start of treatment was approximately the same in the 13-week and 6-month rat study, at 6-7 weeks. The dose levels used in both studies were the same.
Mechanistically, it is known that NO/intracellular cGMP signaling is important for bone growth and remodeling in response to mechanical and hormonal stimuli. Preclinical evidence suggests a concentration-dependent effect of cGMP on long bone growth and remodeling, most relevant to bone growth in in children and adolescents.
Clinical trials for riociguat followed biomarkers of bone metabolism. These showed no apparent effect. While the same monitoring was not included in the vericiguat clinical trials, there was no bone safety effect apparent in the data according to the clinical reviewer. This is consistent with the bone effects manifested in rapidly growing rodent bones but not in bones of mature animals. This suggests that there is minimal risk to adult bones. This comes with the caveat that 1) different bones respond differently to the same chemical stimulus 2) the sampling of bones was minimal 3) loading on bones is very different in a biped versus a quadruped and 4) there was no evaluation of tensile strength of the bones.

The skeletal risk for children is unclear. Based on the mechanism of action and the bone findings in juvenile and adolescent rats with vericiguat and others in this class, an effect on growing bone is possible. Pediatric studies of vericiguat are not planned due to the low frequency of heart failure with a reduced ejection fraction in the pediatric population. The sponsor requested a full waiver for all pediatric age groups (ages 0 to <18 years) under the Pediatric Research Equity Act (PREA). The studies are impossible or highly impractical because the number of pediatric patients is so small or geographically dispersed (section 505B(a)(4)(A)(i) of the Act). The Division agreed to this (Pediatric Study Plan – Initial Agreement entered into DARRTS December14, 2016). (b) (4) . Several clinical trials of riociguat for pulmonary hypertension (PH) in children are ongoing and may provide insight into the possible bone effects. PH itself may have detrimental effects on bone growth.

The safety margins are summarized in the table below. The reviewing toxicologist recommends the use of total AUC rather than the unbound AUC to calculate safety margins. This is based on several considerations. The in vitro protein binding assay was conducted using ultra-filtration in a non-GLP study and showed relatively high inter-subject variabilities. There are also general limitations of using the free fraction(f_u) vs. total drug in calculating safety margins. This includes whether the f_u is the same in animals on the first day of dosing compared to the end of a repeat dose toxicity study or when toxicity is observed. The f_u also doesn't account for changes in plasma protein binding in patients with renal diseases or liver conditions. Using f_u in these situations could inflate the safety margins.

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Safety Margins provided by pivotal general toxicity studies:

Study		NOAEL (mg/kg)	Nonclinical $AUC_{0\text{-}tlast}$ (µg•hr/L)	Safety Margins* (multiples)
6-month rat	Altered liver clinical chemistry and histopathology In both sexes at same dose	30 mg/kg		
	In both sexes at same dose: Increased parathyroid hormone Decreased urinary calcium	30 mg/kg	Males 150000 Females 167000	22X 25X
	Adrenal gland: both sexes showed hyperplasia at same dose	3 mg/kg	Males 13800 Females 16800	2X 2.5X
9-month dog		5	Combined 16000	2.4X

NOAEL = no observed adverse effect level
*Exposure multiples were based on population pharmacokinetics analysis from phase 3 trials, where the maximum clinical dose resulted in systemic geometric mean exposures of $AUC_{0\text{-}24hr}$ of 6680µg•hr/L.

Under the conditions of the studies, vericiguat has not demonstrated genotoxic, carcinogenic, phototoxic, or immunotoxic potential. Consistent target organs of toxicity were the liver, kidney, and adrenals. Inconsistent, somewhat inconclusive signals for endocrine effects were apparent throughout the nonclinical studies. This may be related to the affinity of both parent drug and M1 metabolite for the dopamine transporter (IC50 = 2.9 µM for vericiguat; IC50 not determined for M1). There is also published work suggesting a role for sGC in the hypothalamic-pituitary-adrenal axis.

A suboptimal in vitro assay showed the parent drug to be a moderate inhibitor of the hERG channel with an IC_{50} of 10µM. Although the safety margin of vericiguat on hERG current is high (546-fold), the hERG assay deviates significantly from the new ICH S7B Q&A best practices. Specifically, the study used a different voltage protocol, lacked concentration verification and positive controls (see QT-IRT review in DARRTS dated 8/25/2020). The cardiovascular safety pharmacology in telemetered dogs indicated an effect on the PR interval concurrent with a change in heart rate, possibly an effect on the QRS complex but no effect on QT/QTc intervals. The 13-week dog study showed prolonged QTc intervals in all groups, including control animals in the early portion of the study. The apparent effect abated at later time points. Longer duration dog studies did not show consistent or conclusive QTc effects. The M1 metabolite has not been evaluated for hERG blocking potential. As an N-glucuronide, interaction is unlikely to be significant.

In light of the clinical observation of a trend toward increased mortality and HF hospitalizations in subjects without ICD/CRT/CRT-D devices, more mechanistic information was sought by the Clinical reviewers due to concern for a possible proarrythmic effect. We recommend that vericiguat and the M1 metabolite be evaluated individually for interactions with human cardiac ion channels in order to understand their potential to create arrhythmic effects. This should include, but not be limited to, hINav1.5, hKv11.1(hERG), hKv4.3/hKChIP2.2(hIto),hKv7.1/hKCNE1(hIKs), and hICav1.2. This was communicated to the sponsor as part of the mid-cycle communication sent on September 17, 2020. The data will be analyzed by the Nonclinical reviewer and a review will be documented as an addendum to this review.

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The rabbit embryo-fetal development study suggests an adverse effect of vericiguat on the developing fetus (see table below for the reproductive study safety margins), which can be addressed in labeling. The juvenile animal study conducted in rats showed plasma level exposure similar to adult rats receiving the same dose of BAY1021189. However, the juvenile gastrointestinal tract appeared more sensitive to the pharmacology than the adult GI tract as evidenced by the necrotizing gastroenteritis reported in the juvenile animal study but not the adult toxicology studies. The juvenile animal study results suggest that caution is appropriate for the use of vericiguat in the pediatric population.

Reproductive and Juvenile Toxicity Safety Margins

Study	NOAEL (mg/kg)	Nonclinical exposure	Safety margins[b] (multiples)
Fertility rat *	5	30 mg/m^2	5X on a body surface basis
EFD rat	50	AUC_{0-24} 240000 µg.hr/L	36X
EFD rabbit	0.75	$AUC_{0-tlast}$ 5590 µg.hr/L	0.8X
6-month rat	30 mg/kg	Males 150000 Females 167000	22X 25X
PPND rat*	7.5 (LOAEL)	45 mg/m^2	7X on a body surface basis
Juvenile rat	1 mg/kg (LOAEL for ↓ serum Mg in males)	$AUC_{0-tlast}$ 8430 µg.hr/L	1.3X
	10 mg/kg for necrotizing enteritis	$AUC_{0-tlast}$ 34800 µg.hr/L	5X

EFD = embryo-fetal development; NOAEL = no observed adverse effect level; PPND = peri- and postnatal
* no toxicokinetics conducted
a. Total plasma AUC is used
b. Exposure multiples were based on population pharmacokinetics analysis where a 10 mg QD clinical dose resulted in systemic exposures of AUC_{0-24hr} = 6680 µg•hr/L or 6 mg/m^2 on a body surface area for a 60 kg patient.

1.3 Recommendations

1.3.1 Approvability

From the nonclinical perspective, vericiguat is approvable.

1.3.2 Additional Non Clinical Recommendations

1.3.3 Labeling

8.1 Pregnancy

Risk Summary

There are no data (b) (4) TRADEMARK in pregnant women. (b) (4) In a

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pre/postnatal toxicity study, vericiguat administered orally to rats during gestation through lactation (b) (4) (b) (4) maternal toxicity (b) (4), which resulted in decreased pup body weight gain (≥ (b) (4) times the MRHD) and pup mortality ((b) (4) times the MRHD) during the preweaning period *(see Animal data).*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal data

In a prenatal developmental toxicity study in rats, vericiguat was administered orally to pregnant rats during the period of organogenesis from gestation days (GD) 6 to 17 at doses of 5, 15 or 50 mg/kg/day. No developmental toxicity was observed up to the highest dose (36 times the human exposure at the MRHD, total AUC). (b) (4) maternal toxicity (decreased body weight gain and food consumption) was observed at ≥15 mg/kg/day (≥10 times the human exposure at the MRHD). There was no maternal toxicity at 5 mg/kg/day (4 times the human exposure at the MRHD).

In (b) (4) study in rabbits, vericiguat was administered orally to pregnant rabbits during the period of organogenesis from GD 6 to 20 at doses of 0.75, 2.50 or 7.50 mg/kg/day. (b) (4) (decreased food consumption and body weight loss) (b) (4) late spontaneous abortions and resorptions was noted at ≥2.50 mg/kg/day (b) (4) times the human exposure at the MRHD). There was no maternal toxicity or abortions/resorptions (b) (4) to the human exposure at the MRHD.

In a pre-postnatal development study in rats, vericiguat was administered orally at doses of 7.5, 15 or 30 mg/kg/day from GD 6 through lactation day 21. (b) (4) maternal toxicity (decreases in food consumption and body weight gain) was observed at all dose levels (≥ (b) (4) times the human exposure at the MRHD) and resulted in decreased pup body weight gain at ≥15 mg/kg/day (≥21 times the human exposure at the MRHD) and pup mortality at 30 mg/kg/day (49 times at the MHRD). (b) (4)

[^{14}C]-vericiguat was administered orally to pregnant rats at a dose of 3 mg/kg. Vericiguat-related material was transferred across the placenta, with fetal plasma concentrations of approximately 67% maternal concentrations on GD 19.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity was evaluated in 2-year studies conducted in CD1 mice and Wistar rats. Vericiguat did not show a carcinogenic effect in mice dosed up to 150 mg/kg/day (males) or up to 250 mg/kg/day (females). These doses were associated with exposures (b) (4) (males) or 78 (females) times the human exposure (total AUC) at the MRHD of 10 mg/day.

In the carcinogenicity study in rats, no vericiguat-related tumor or hyperplastic findings were (b) (4) exposures of (b) (4) males and 21x in females the human exposure at the MRHD.

Mutagenesis

Vericiguat was not genotoxic in the *in vitro* microbial mutagenicity (Ames) assay, the *in vitro* mouse lymphoma assay and the *in vivo* rat and mouse micronucleus assay.

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Impairment of Fertility

There were no effects on fertility, mating performance or early embryonic development when vericiguat was administered to rats at (b) (4) times the MRHD. (b) (4)

13.2 Animal Toxicology and/or Pharmacology

In growing rats, reversible effects on bone formation were observed, consisting of hypertrophy of growth plate and hyperostosis and remodeling of metaphyseal and diaphyseal bone. These effects were not observed after chronic administration of vericiguat (b) (4) up to 22X in male rats, 25X in female rats and 2.4X in dogs, (b) (4) the human exposure at the MRHD (total AUC).

2 Drug Information

2.1 Drug

CAS Registry Number: 1350653-20-1

Generic Name: vericiguat

Code Name: BAY1021189, MK1242

Chemical Name

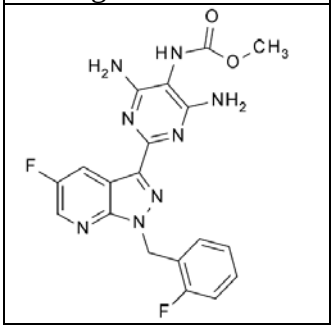
Chemical name / IUPAC	Methyl {4,6-diamino-2-[5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl}carbamate
Other names	Methyl N-[4,6-diamino-2-[5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl]carbamate
	Methyl [4,6-diamino-2-[5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl]carbamate

Molecular Formula/Molecular Weight: $C_{19}H_{16}F_2N_8O_2$/ 426.39

Reference ID: 4679731

Structure or Biochemical Description:

vericiguat



Pharmacologic Class: soluble guanylate cyclase (sGC) stimulator

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND116743

2.3 Drug Formulation

2.5 mg tablet		5 mg tablet		10 mg tablet	
Composition	**Amount (mg)**	**Composition**	**Amount (mg)**	**Composition**	**Amount (mg)**
Drug substance		**Drug substance**		**Drug substance**	
Vericiguat (b) (4)	2.50	Vericiguat (b) (4)	5.00	Vericiguat (b) (4)	10.00
Excipients	(b) (4)	**Excipients**	(b) (4)	**Excipients**	(b) (4)
Cellulose microcrystalline		Cellulose microcrystalline		Cellulose microcrystalline	
Croscarmellose sodium		Croscarmellose sodium		Croscarmellose sodium	
Hypromellose (b) (4)		Hypromellose (b) (4)		Hypromellose (b) (4)	
Lactose monohydrate		Lactose monohydrate		Lactose monohydrate	
Magnesium stearate		Magnesium stearate		Magnesium stearate	
Sodium laurilsulfate (b) (4)		Sodium laurilsulfate (b) (4)		Sodium laurilsulfate (b) (4)	
Weight (uncoated tablet)		**Weight (uncoated tablet)**		**Weight (uncoated tablet)**	
Film-coating (b) (4)		**Film-coating** (b) (4)		**Film-coating** (b) (4)	
Hypromellose (b) (4)		Ferric oxide red [d]		Ferric oxide yellow [d]	
Talc		Hypromellose (b) (4)		Hypromellose (b) (4)	
Titanium dioxide [d] (b) (4)		Talc		Talc	
Weight (film-coating)		Titanium dioxide [d] (b) (4)		Titanium dioxide [d] (b) (4)	
Weight (coated tablet)	**124.00**	**Weight (film-coating)**			
		Weight (coated tablet)	**124.00**		

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2.4 Comments on Novel Excipients

All excipients are of compendial quality.

2.5 Comments on Impurities/Degradants of Concern

These have been resolved during the development process. There are no new impurities of toxicological concern, which was confirmed with the CMC reviewer.

2.6 Proposed Clinical Population and Dosing Regimen

To be used in patients following a worsening heart failure event in adults with symptomatic chronic heart failure and ejection fraction less than 45%, in combination with other heart failure therapies. The recommended starting dose is 2.5 mg once a day, taken with food. The dose is to be doubled every two weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient.

2.7 Regulatory Background

A tabular summary of the nonclinical reviews and memos to the file for the IND116743 is appended to this review. There were several nonclinical issues that the Division asked the sponsor to clarify during the IND process. These included urinary crystals, prolonged melanin-binding and possible effects on the substantia nigra, and findings in the 13-week juvenile animal study suggesting an effect on development of the reproductive systems.

3 Studies Not Reviewed

All of the nonclinical studies required by ICH recommendations have been previously reviewed (i.e., during the IND stage) and reviews are available in DARRTS.

4 Pharmacology

BAY1021189 is a soluble guanylate cyclase (sGC) stimulator proposed for chronic heart failure. A failing heart does not maintain the cardiac output needed to meet peripheral demands. The physiologic compensation of neurohormonal responses includes increased sympathetic nervous tone, attenuated vagal tone, renin-angiotensin-aldosterone system activation, and release of antidiuretic hormone/arginine vasopressin. The net result of these neurohormonal responses is increased vascular volume from Na+ and water retention, increased thirst and increased vascular tone. Other manifestations are vasoconstriction with increased peripheral vascular resistance, increased ventricular preload and afterload. Chronic manifestation of these compensatory mechanisms accelerates deterioration of cardiac function and promotes pathologic remodeling.

On a cellular level, the disease process disrupts signaling within the NO-sGC-cGMP pathway, leading to endothelial function disruption, hypothesized to be a predominant cause of the dysregulation of vascular tone. The pharmacological rationale for this NDA is that stimulation of soluble guanylate cyclase in vascular smooth muscle will result in vasodilation, reduced vascular tone and reduced cardiac afterload, slowing the pathologic processes of heart failure.

4.1 Primary Pharmacology

The primary pharmacology was demonstrated in vitro using recombinant sGC and measuring enzymatic activity as a function of [^{32}P]cGMP formed from α[^{32}P]-GTP. This showed an

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increased dependence on the concentration of DEA/NO added to vericiguat. Vericiguat did not stimulate heme-free sGC. Vericiguat was also evaluated in a Chinese hamster ovary (CHO) cell line over expressing rat sGC and showed an EC_{50} value of 1005nM. The human major circulating metabolite M-1 showed no stimulation of sGC up to 10 µM, in the same assays. In an in vitro luminometric GTP-consumption assay the minimal effective concentration reported for BAY1021189 was 120 nM.

In vitro testing showed minimal, if any interaction, of BAY1021189 with either receptor guanylate cyclase (GC)-A or receptor GC-B (natriuretic peptide receptors), supporting specificity for soluble GC. The drug inhibited platelet aggregation in human platelet rich plasma (PRP) and washed platelets. In response to ADP and TRAP-6 stimulation in PRP, the IC_{50} ranged from 34 to19µM respectively. The sponsor presented data also suggesting direct stimulation of the vasodilator-stimulated phosphoprotein (VASP) pathway, contributing to platelet aggregation inhibition.

4.2 Secondary Pharmacology

The receptor binding studies indicated interaction with PDE4 (24%), UDP glucuronosyltransferase (UGT1A1) (45%), the dopamine transporter (DAT) (65%), adenosine A2 (40%), and bradykinin B2 (-24), when tested at 10 µM. The IC_{50} for the DAT was reported as 2.9µM.
The major circulating metabolite, M1, an N-glucuronide referred to as BAY1222707, has also been evaluated as far as in vitro pharmacology. This metabolite constituted approximately 70% of circulating drug-related material in humans and approximately 10% in the nonclinical species. As this is an N-glucuronide rather than an acyl-glucuronide, there is less likelihood of significant pharmacologic or toxicologic activity although M1 has some similarity to the parent drug in off-target activity, having mild (approximately 30%) affinity for the dopamine transporter.

4.3 Safety Pharmacology

The hERG assay showed concentration dependent inhibition of the tail current amplitude that was statistically significant at concentrations ≥1µmol (approximately 14% inhibition, $p<0.01$ vs the pre-drug controls). The effects were partially reversible upon washout of the test substance. Fifty percent inhibition was achieved at a concentration of 10µM making vericiguat a relatively weak hERG inhibitor.

Telemetry studies conducted in normotensive and spontaneously hypertensive rats, conscious dogs, anesthetized normoxic dogs, anesthetized acutely hypoxic dogs with autonomic blockade, and anesthetized dogs with pacing-induced heart failure showed consistent dose-related decreased mean blood pressure, with a compensatory increase in heart rate. Maximal effects usually occurred within 8 hours after administration. The duration of the reduced blood pressure depended upon the dose, with higher doses having a longer persistence of effect. Conscious telemetered Beagles showed a dose-related prolongation of PR interval by approximately 20% of baseline. There were no signs of QT/QTc prolongation observed with vericiguat in telemetered Beagle dogs up to 26-fold the human plasma Cmax at the MRHD. The LOEL was identified as the lowest dose tested of 0.6 mg/kg (AUC_{0-24} 2274 µg.h/L). Dose related decreases in systolic

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and aortic blood pressure were identified. There also appeared to be a rebound effect of increased blood pressure starting approximately 14 hours after administration of drug. The observation period did not extend long enough to see a return to baseline.

Neurologic findings in the CNS safety pharmacology included splayed hindlimbs (≥5 mg/kg; AUC_{0-24} 10125 µg.hr/l), at 15 mg/kg (AUC_{0-24} 54706 µg.hr/l), ptosis, “slow deliberate gait”, decreased activity, and delayed righting reflex were observed. The blood pressure effects confound the ability to determine primary neurologic effects versus effects secondary to cerebral ischemia. However, similar effects were also reported in both rat and dog toxicology studies and were not completely reversed at the end of the two-week, drug-free, recovery period of the rat study.

Gastrointestinal movement of ingesta was decreased. A maximum effect of -18% relative to the control animals was reported at the highest dose of 15mg/kg. Gastric emptying did not appear to be affected.

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5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Analytical methods

Vericiguat and M1 concentrations in plasma were determined by high pressure liquid chromatography and mass spectrometry (LC-MS/MS) after protein precipitation. The assays used for vericiguat and M1 had the following ranges:

Species	vericiguat		M1	
	LLOQ	ULOQ	LLOQ	ULOQ
Mouse	1-5 ng/ml	1000ng/ml	2 ng/ml	1000ng/ml
Rat	1-5 ng/ml	1000ng/ml	5 ng/ml	1000ng/ml
Rabbit	1-5 ng/ml	1000ng/ml	Not done	
Dog	1-5 ng/ml	1000ng/ml	Not done	

Absorption
After single intravenous and peroral doses of BAY1021189 (0.03 and 0.3 mg/kg respectively) administered to dogs, maximum plasma concentrations were reached by 1.0 to 1.8 hours after dosing. Absolute bioavailability ranged from 72-75% in dogs and 40-50% in rats. In humans, oral bioavailability is reported as 93%. Mean plasma elimination half-lives were 5.4-7 hours, independent of the route of administration.

Distribution
Plasma protein binding as determined by ultrafiltration was determined to be relatively similar across species and was moderate to high. The fraction unbound was reported as 2.18% in human, 3.69% in rabbit, 4.55% in rat, 5.55% in monkey, 7.99% in mouse, and 10.2% in dog (see Sponsor table below). Albumin was the major binding protein.

Protein binding was independent of concentration in the range of 0.2 to 2.2 µM (clinically relevant concentration range). In humans, plasma protein binding did not change with renal or hepatic impairment.

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Table 1: Extent of binding of BAY 1021189 to plasma proteins of selected species. Free fraction [f_u] was determined by ultrafiltration using [^{14}C]BAY 1021189. Arithmetic means of n=3 incubations per concentration

Species	Concentration in plasma [µg/L]	f_u [%]	f_u mean [%]	CV [%]
Rat, male	93.1	3.80		
Rat, male	930	3.99		
Rat, male	9425	5.87	4.55	25.1
Mouse, male	93.2	7.19		
Mouse, male	957	7.29		
Mouse, male	9327	9.50	7.99	16.3
Dog, female	93.8	9.50		
Dog, female	949	9.55		
Dog, female	9234	11.4	10.2	10.8
Rabbit, female	94.3	3.11		
Rabbit, female	984	3.04		
Rabbit, female	9078	4.92	3.69	28.9
Monkey, female	93.5	4.66		
Monkey, female	943	4.65		
Monkey, female	9278	7.33	5.55	27.9
Human, male[a]	92.3	2.00		
Human, male[a]	936	2.35	2.18	11.4
Human, male[a]	9395	4.05		
Human V1, male	909	2.31		
Human V2, male	932	3.02		
Human V3, male	918	2.53		
Human V4, male	939	2.55		
Human V5, male	889	2.51	2.58	10.1

a = pooled plasma n=3
CV = coefficient of variation
V = healthy volunteer, individual determination

Quantitative whole body autoradiography showed the highest concentrations of radioactivity in the kidneys, adrenal glands, and liver. Radioactivity was also detected in the bone, bone marrow and brain, but to a much lesser extent than what was reported for blood. The half-life of [^{14}C]BAY1021189 in pigmented skin was 344 hours and in the retinal pigmented epithelium was 161 hours after a single dose.

Metabolism

[^{14}C] BAY1021189 was incubated in vitro with liver microsomes of Wistar rat, Beagles, Cynomolgus monkeys, CD-1 and NMRI mice, Himalayan rabbit and human. In vitro microsomes showed low turnover of vericiguat in all species. The primary reactions were hydroxylations and oxidative dealkylation. In hepatocytes, N-glucuronidation of parent compound was a major pathway. This produced the M1 metabolite, a major human metabolite.

The biotransformation of vericiguat in the rat was examined in plasma, urine, feces, and bile of Wistar rats. The metabolites identified were N-glucuronide (M1, accounting for 1.6% of AUC of total radioactivity), de-benzylated metabolite M2, hydroxylated metabolites M3(1% of total AUC radioactivity), M4, M5; hydroxyl-glucuronides M10,

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M11, hydroxysulfate M12, acetylated metabolite M15 and glutathione derivative M16. Parent drug accounted for 97% of total AUC.

The following metabolites were identified in the dog: N-glucuronide(M1), debenzylated (M2), hydroxylated (M3), and metabolite M12 formed by hydroxylation and sulfation. Vericiguat accounted for >90% of the total plasma radioactivity while M1 accounted for ~2%.

The only metabolite identified in the plasma of the mouse is the M1 metabolite. Similar to other species, vericiguat accounted for ~99% of AUC and the M1 accounted for the remainder.

In human plasma, vericiguat and the M1 metabolite were the only detectable drug-related material. Vericiguat represented on average 26.6% of AUC and the metabolite accounted on average for 72.1% AUC of total radioactivity.

Excretion

Absorption and excretion were examined in male Wistar rats after single intravenous and oral administration of[^{14}C]BAY1021189. Seven days after IV and oral administration, 76% and 81% of administered radioactivity had been recovered in the feces. Urinary excretion was 21% and 11% respectively. No radioactivity was detected as ^{14}CO2 within 24 hours after oral administration of [^{14}C]-vericiguat.

Reviewer's Summary of Excretion of Administered Radioactivity

	Intravenous administration			Oral administration		
	Bile	feces	urine	Bile	feces	urine
Bile duct cannulated	43%		15%	35%	36%	10%
	33% found in GI contents			9% found in GI contents		
Intact rats		76%	21%		81%	11%

Overall, vericiguat is excreted by multiple routes that include glucuronidation to M1, glomerular filtration of parent drug, biliary/fecal excretion, and a minor amount of oxidative metabolism.

5.2 Toxicokinetics

Several pivotal studies are considered here.
<u>28-day repeat dose toxicology study in rats:</u>

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Day 1, the increase in AUC from one dose to the next was roughly proportional. There was slightly greater plasma level of the parent drug in the females. From day1 to day 22, an increase in AUC in both sexes is apparent at all doses.

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Day 1							
males					females		
		15mg/kg	30 mg/kg	60 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg
AUC(0-24)	[µg·h/L]	49942	107238	210719	55058	138902	23435
$AUC(0\text{-}24)_{norm}$	[kg·h/L]	3.33	3.57	3.51	3.67	4.63	3.91
C_{max}	[µg/L]	4710	7489	10175	4979	8319	11338
$C_{max,norm}$	[kg/L]	0.314	0.250	0.170	0.332	0.277	0.189
$C(24)/C_{max}$	[%]	4.27	18.0	81.0	6.82	39.5	78.9
t_{max}	[h]	4.00	7.00	7.00	4.00	7.00	2.00

The increase in plasma level with increasing dose is proportional from 15mg/kg to 30 mg/kg. The increase in AUC from 30 mg/kg to 60 mg/kg is less than proportional. There is no apparent difference in AUC between the sexes.

Day 22							
Sex			**Male**			**Female**	
Dose	[mg/kg]	15	30	60	15	30	60
AUC(0-24)	[µg·h/L]	74606	151914	240246	86430	157916	252674
$AUC(0\text{-}24)_{norm}$	[kg·h/L]	4.97	5.06	4.00	5.76	5.26	4.21
C_{max}	[µg/L]	8004	16042	23602	8982	15583	24258
$C_{max,norm}$	[kg/L]	0.534	0.535	0.393	0.599	0.519	0.404
$C(24)/C_{max}$	[%]	2.05	1.87	3.28	1.80	2.87	2.76
t_{max}	[h]	4.00	7.00	7.00	7.00	4.00	7.00
Multiple of Day 22 rat AUC to clinical AUC at MRHD (6680 µg hr/l)		11X	23X	36X	13X	24X	38X

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6-month repeat dose rat study:

The increases in exposure from one dose to the next are roughly proportional. There was an increase in exposure (accumulation) from Day 1 to day 149. The sponsor proposed that the lower AUC in males was due to greater CYP450 activity.

Day 1		males			females		
		3mg/kg	10 mg/kg	30 mg/kg	3mg/kg	10 mg/kg	30 mg/kg
AUC(0-tlast)	µg·h/L	8390	29000	95500	13200	44500	130000
AUC(0-tlast)norm	kg·h/L	2.80	2.90	3.18	4.40	4.45	4.35
tlast	h	24.0	24.0	24.0	24.0	24.0	24.0
Cmax	µg/L	791	2670	6080	1100	3330	7310
Cmax,norm	kg/L	0.264	0.267	0.203	0.368	0.333	0.244
tmax	h	7.00	4.00	4.00	7.00	7.00	7.00
C(tint)/Cmax	%	4.6	7.8	43.3	11.8	19.1	47.5
t(int)	h	24.0	24.0	24.0	24.0	24.0	24.0
Day 149							
AUC(0-tlast)	µg·h/L	13800	45000	150000	16800	62600	167000
AUC(0-tlast)norm	kg·h/L	4.59	4.50	5.01	5.60	6.26	5.57
tlast	h	24.0	24.0	24.0	24.0	24.0	24.0
Cmax	µg/L	1360	4700	12500	1530	6000	18400
Cmax,norm	kg/L	0.454	0.470	0.415	0.509	0.600	0.613
tmax	h	2.00	4.00	2.00	4.00	4.00	4.00
C(tint)/Cmax	%	2.8	4.9	7.0	6.0	4.8	4.3
t(int)	h	24.0	24.0	24.0	24.0	24.0	24.0
Multiple of Day 149 rat AUC to clinical AUC at MRHD (6680 µg.hr/l)		2X	6.7X	22X	2.5X	9.4X	25X

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The increase in AUC from the mid-dose to the high dose was less than dose proportional, suggesting possible saturation. Three was no consistent change in exposure over time.

28-day repeat dose study in dogs

Day 1, combined male and female values				
		2.5 mg/kg	7.5 mg/kg	25 mg/kg
AUC(0-tlast)	µg·h/L	6360	15900	16700
AUC(0-tlast)norm	kg·h/L	2.54	2.13	0.668
tlast	h	24.0	24.0	24.0
Cmax	µg/L	969	2620	2020
Cmax,norm	kg/L	0.388	0.350	0.0809
tmax	h	0.891	0.891	1.26
C(tint)/Cmax	%	3.0	2.8	5.2
t(int)	h	24.0	24.0	24.0
Day 25, combined male and female values				
AUC(0-tlast)	µg·h/L	6390	14100	17600
AUC(0-tlast)norm	kg·h/L	2.56	1.88	1.17
tlast	h	24.0	24.0	24.0
Cmax	µg/L	939	2220	2630
Cmax,norm	kg/L	0.376	0.296	0.175
tmax	h	0.891	0.630	0.871
C(tint)/Cmax	%	3.5	3.8	4.2
t(int)	h	24.0	24.0	24.0
Multiple of Day 25 dog AUC to clinical AUC at MRHD (6680 µg.hr/l)		1X	2X	2.6X

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39-week repeat dose study in dogs:
There was a decrease in AUC at the highest dose from the day 91 value to day 273. Otherwise, the AUC values show little change over the course of the study.

Day 1 combined male and female values				
		0.5 mg/kg	1.5 mg/kg	5 mg/kg
AUC(0-tlast)	µg·h/L	2050	5940	16000
AUC(0-tlast)norm	kg·h/L	4.10	3.96	3.19
tlast	h	24.0	24.0	24.0
Cmax	µg/L	345	890	2160
Cmax,norm	kg/L	0.690	0.593	0.432
tmax	h	0.545	0.707	1.30
C(tint)/Cmax	%	3.9	4.5	5.5
t(int)	h	24.0	24.0	24.0
Day 91 combined male and female values				
AUC(0-tlast)	µg·h/L	1820	6000	16000
AUC(0-tlast)norm	kg·h/L	3.63	4.00	3.21
tlast	h	24.0	24.0	24.0
Cmax	µg/L	264	862	2160
Cmax,norm	kg/L	0.528	0.574	0.433
tmax	h	0.648	0.917	1.09
C(tint)/Cmax	%	4.6	5.4	6.5
t(int)	h	24.0	24.0	24.0
Day 273 combined male and female values				
AUC(0-tlast)	µg·h/L	2380	7200	12000
AUC(0-tlast)norm	kg·h/L	4.76	4.80	2.40
tlast	h	24.0	24.0	24.0
Cmax	µg/L	327	934	1490
Cmax,norm	kg/L	0.654	0.623	0.299
tmax	h	0.707	0.771	1.00
C(tint)/Cmax	%	5.3	6.3	6.1
t(int)	h	24.0	24.0	24.0
Multiple of Day 273 dog AUC to clinical AUC at MRHD (6680 µg.hr/l)		0.36X	1X	1.8X

6 General Toxicology

6.2 Repeat-Dose Toxicity

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The target organs of toxicity in nonclinical studies have consistently been liver (decreased synthetic capacity, altered triglycerides, etc. measurable in standard clinical chemistry), kidney and adrenal glands. The sponsor proposes that the alterations to adrenal function and histopathology are due to the cyclic changes in blood pressure and subsequent activation of the renin-angiotensin-aldosterone axis. This would also engage the kidney. It's a reasonable hypothesis and could potentially be supported with measurement of some of the circulating components of the system.

Early in development, urinary crystals were reported for both rats and dogs. These were insoluble crystals described as resembling sea urchins. The sponsor was asked to characterize this phenomenon. The sponsor speculated that the crystals were re-crystallization of renally excreted vericiguat. The lowest plasma concentration at which the crystals were reported was $AUC_{(0-24)}$ 45000µg.h/L. The human AUC for a 10 mg dose was reported at this point in development as 9128 µg.h/L. The table below includes the current AUC_{0-24} for heart failure patients at steady state. To summarize the relative exposure between species, the following table is presented:

Reviewer's summary of relative plasma exposure of vericiguat

	Daily dose	Total exposure		Fraction unbound	
		Cmax µg/L	($AUC_{(0-24)}$) µg.hr/L)	Cmax µg/L	($AUC_{(0-24)}$) µg hr/L)
rat	10 mg/kg/day	4700	45000	183	1755
Human*	10 mg/day	284	9128	6.2	199
human‡	10 mg/day		6680		
*human AUC available at that point in development ‡human AUC from heart failure patients at steady state					

Using total AUC exposure, there is a five-fold concentration difference between human and rat plasma concentrations. The clinical single dose escalation study (Study 15355, PH 37029) and multiple dose escalation study (Study 15357, PH 37952) of vericiguat showed no drug-related increase or change of urinary sediments. Non-defined crystals were not detected in spontaneous urine samples. In the clinical renal impairment study (Study 15813, PH38785) the sponsor reported no crystals found in the urine sediment analysis in spontaneously obtained urine samples. Via email, the Medical Officer for this IND noted that no urinary-related AEs were apparent at that point in development. At the time of the NDA review, we have more extensive patient experience to evaluate and this nonclinical signal maybe addressed with clinical data. The sponsor also noted that the amount of vericiguat excreted into human urine is approximately 40-fold lower than in the rat at the lowest dose associated with urinary crystals. This is below the limit of solubility of vericiguat in buffered aqueous solutions.

There were no signals for new hazards or new target organs of toxicity in the chronic toxicology studies. In the six-month rat toxicology study, suggestions of altered liver and/or adrenal function and bone metabolism appeared in the clinical chemistry. The urinalysis reported the sea urchin-like sediment similar to that reported in the original toxicology studies at doses greater than or equal to 10 mg/kg. "Bright yellow droplets" were reported in one control animal and all drug-treated groups. Increased mean normalized prostate weight was reported for all doses of drug-treated males.

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The 13-week and 39-week dog toxicology studies included ECG assessments. The 13-week study showed inconsistent increases in the QTcF interval in all groups including the control animals. The 39-week study showed at one time point mild, inconsistent increases with no discernible dose-relationship. Both the 13-week and 39-week QT findings could reasonably be attributed to normal variability.

The 39-week dog study included histopathological analysis of the substantia nigra, motivated by the prolonged melanin binding of the parent drug. One mid-dose male was reported to have focal necrosis of that tissue. The change was described as minimal with no opinion from the pathologist as to the significance.

7 Genetic Toxicology

BAY1021189 was evaluated in the bacterial reverse mutation assay, an in vitro mouse lymphoma cell assay, and in vivo clastogenicity (rodent micronucleus). All assays were negative except for the rodent micronucleus in which a weak positive result was reported. This was followed up with an in vivo micronucleus assay incorporated into the 6-month rat study. This second in vivo assay showed no increase in micronucleated erythrocytes associated with drug administration.

7.2 Other Genetic Toxicity Studies

N/A

8 Carcinogenicity

The complete review of the carcinogenicity studies may be found in DARRTs (entered July 1, 2020) as well as the minutes of the Executive Carcinogenicity Assessment Committee (Exec CAC) discussion of the results (entered July1, 2020).
A consideration for both the rat and mouse studies is the relative proportions of the M1 metabolite. This is an N-glucuronide that accounts for 70% of human plasma exposure and in rat and mouse accounts for less than 10% of total exposure, reaching <0.24X the human AUC. This was discussed with the Executive CAC at the time the protocols were presented. These was limited pharmacological information at that time. However, the Committee noted that as the metabolite is an N-glucuronide and not an acyl-glucuronide, there was a relatively lower level of concern. The Executive CAC determined that if the M1 metabolite was synthesized and administered, it was not likely to remain intact during passage through the stomach. Therefore, additional synthesis and administration of the compound was not likely to add to the informative value of the studies.

The original doses for carcinogenicity studies in both rats and mice proposed by the sponsor were based on pharmacokinetics and greater than 25-fold the human systemic exposure of non-protein bound drug. The Exec CAC noted that greater than 25-fold the human exposure based on unbound drug was not appropriate in this case, since the unbound fraction of drug is greater in rodents than in humans and small differences inflated the ratio. The Exec CAC recommended that a comparison of total plasma exposure of drug is more appropriate.

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For the rat study, dose limiting neurologic toxicity was observed in the safety pharmacology and 4-week repeat dose study and was recommended by Exec CAC to be the basis for the high dose selection. The mid and low doses were identified to provide adequate dose-spacing based on AUC values. . A combination of the dose limiting toxicity and pharmacokinetics was used as the basis for dose selection. When the Exec CAC reviewed the sponsor's protocol, a qualified concurrence with the proposed doses was given. This was due to the conduct of the carcinogenicity studies at different facilities from the preliminary studies and the use of animals from a different supplier. The Exec CAC noted that studies might not be acceptable if toxicities were significantly different due to the differences in study location and animal source from those in the preliminary studies, such that the dose selection would have been altered.

The interpretation of the rat carcinogenicity study was that it was GLP compliant, adequate and negative for demonstrating carcinogenic potential. Overall mortality was not affected in either sex of rat. No new toxicities or target organs were apparent. Adrenal medullary hyperplasia and pheochromocytomas were noted in both sexes of rats at different incidences. Leydig cell adenomas were noted in the male rats. Both parent drug and the main metabolite M1 have affinity for the dopamine transporter, possibly underlying the testicular tumors. The CDER statistical reviewer's draft review did not find statistical significance for either a dose-response trend ($p<0.005$) or a pairwise comparison($p<0.01$) for either of these common tumors. Pheochromocytomas are more commonly seen in male rather than female rats. The incidences of both tumor types were outside the range of historical control values for both the control and drug-treated groups of the definitive study. The findings for the ovaries included atrophy, cysts, and decreased or absent follicles but no tumors.

From FDA Statistical Review (in DARRTS dated 7/6/2020, under IND-116743)

Table 2: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons
Treated Groups and Control Group in Rats

Sex	Organ Name	Tumor Name	0 mg Cont (N=60) P - Trend	0mg Water Cont (N=60)	2 mg Low (N=60) P - C vs. L	6 mg Med (N=60) P - C vs. M	20 mg High (N=60) P - C vs. H
Male	Adrenal	B-Phaeochromocytoma, Benign	4/60 (51) 0.0183@@	2/60 (53) NC	4/60 (52) 0.6532	6/60 (53) 0.3955	10/60 (50) 0.0686
		B-Phaeochromocytoma, Benign / M-Phaeochromocytoma Malignant	4/60 (51) 0.0210@@	3/60 (53) NC	4/60 (52) 0.6532	7/60 (53) 0.2856	10/60 (50) 0.0686
	Testis	B-Adenoma, Leydig Cell	2/60 (51) 0.0076@@	0/60 (53) NC	1/60 (52) 0.8822	0/60 (52) 1.0000	6/60 (50) 0.1281

@@: not Statistically significant at 0.005 for common tumor in dose response relationship

Historical Controls

- Adrenal pheochromocytoma:0-2
- Testis Leydig cell tumor:0-3

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Reviewer's summary of findings in female rats (n=60 examined per group)

Adrenal Findings					
Vericiguat mg/kg/day	0	0	2	6	20
Adrenal Medullary hyperplasia	3	2	2	0	12
Adrenal pheochromocytoma, benign	0	2	1	1	0
Ovarian Findings					
Ovarian atrophy	4	2	1	4	9
Cyst	21	15	10	30	26
Decreased number/absent follicles	20	11	14	23	32
Historical control range for all ovarian findings was reported as 0					

Reviewer's summary of rat exposure to Vericiguat (MRHD 10 mg) and M1 relative to human‡

Male rats			
Dose mg/kg/day	2	6	20
$AUC_{0\text{-last}}$ day 387(µg.hr/ml) Vericiguat (BAY1021189)	12500	36800	105000
Multiple of human AUC 10 mg vericiguat	1.7x	5x	14x
$AUC_{0\text{-last}}$ day 387(µg.hr/ml) M1 (BAY1222707)	508	2199	9010
Multiple of human AUC 10 mg M1	<0.24	<0.24	<0.24
Female rats			
Dose mg/kg/day	2	6	20
$AUC_{0\text{-last}}$ day 387(µg.hr/ml) Vericiguat (BAY1021189)	16500	44400	139000
Multiple of human AUC 10 mg vericiguat	2.2x	6x	19x
$AUC_{0\text{-last}}$ day 387(µg.hr/ml) M1 (BAY1222707)	366	2680	8420
Multiple of human AUC 10 mg M1	<0.24	<0.24	<0.24

‡Day 387 was the greatest reported exposure based on AUC.

Healthy human volunteers (mean values)	Cmax µg/L	AUCτ
Vericiguat 10 mg steady state	398	7320 µg hr/L
M1	1610	38,000µg hr/L

A pharmacokinetic rationale (> 25-fold human exposure based on total AUC) was used for the mouse carcinogenicity study dose selection and received Exec CAC concurrence
Similar to the rat study, the Exec CAC noted that due to the differences in location of facilities conducting the supporting studies and sourcing the animals, the study might not be acceptable if there were significant differences in toxicities that would have necessitated different dose selection.

The mouse study was also interpreted to be GLP compliant, adequate, and negative for carcinogenic potential. The doses used were those with which the Exe CAC concurred and survival was unaffected with adequate numbers of animals for examination at the termination of the study. A maximally tolerated dose was achieved in the females given the high dose of 250 mg/kg/day as they gained on average 19% less than the control group over the course of the study. No new toxicities or target organs were observed.

The FDA statistical review did not find either the trend test($p<0.005$) or pairwise comparison ($p<0.01$) to be statistically significant for common tumors. The trend test for the rare tumor also did not reach significance ($p<0.025$) and neither did the pairwise comparison ($p<0.05$).

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Table 4: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons
Treated Groups and Control Group in Mice

Sex	Organ Name	Tumor Name	0 mg Cont (N=60) P - Trend	5 mg Low (N=60) P - VC vs. L	15 mg Med (N=60) P - VC vs. M	50 mg Med-High (N=60) P - VC vs. MH	150 mg High (N=60) P - VC vs. H
Male	Haemolympho-Reticular System	M-Malignant Lymphoma-Lymphoblastic	0/60 (49) 0.0290@@	0/60 (48) NC	0/60 (44) NC	1/60 (45) 0.4787	2/60 (45) 0.2265
	Liver	B-Hepatocellular Adenoma/ M-Hepatocellular Carcinoma	8/60 (50) 0.8439	15/60 (50) 0.0765	16/60 (49) 0.0442@	8/60 (45) 0.5159	8/60 (44) 0.4961
Sex	**Organ Name**	**Tumor Name**	**0 mg Cont (N=60) P - Trend**	**6 mg Low (N=60) P - VC vs. L**	**20 mg Med (N=60) P - VC vs. M**	**60 mg Med-High (N=60) P - VC vs. MH**	**250 mg High (N=60) P - VC vs. H**
Female	Harderian Gland	B-Adenoma	2/60 (31) 0.9974	3/60 (35) 0.5585	10/60 (37) 0.0261@	0/60 (34) 1.0000	0/60 (35) 1.0000
	Ovary	B-Tubulostromal Adenoma	0/60 (30) 0.0366@@	0/59 (33) NC	0/59 (33) NC	1/60 (35) 0.5385	2/60 (35) 0.2861
	Uterus	B-Polyp, Endometrial Stromal	1/60 (30) 0.6025	8/60 (36) 0.0271@	8/60 (36) 0.0271@	3/60 (36) 0.3789	5/60 (37) 0.1543

@@: not Statistically significant at levels of 0.005 and 0.025 for common and rare tumors respectively in dose response relationship
@: not Statistically significant at 0.01 for common tumor in pairwise comparison

Reviewer's summary of mouse exposure to Vericiguat and M1 relative to human:

Male mice				
Dose mg/kg/day	5	15	60	150
$AUC_{0\text{-last}}$ day 387(µg.hr/ml) Vericiguat (BAY1021189)	15100	49100	175000	397000
Multiple of human AUC 10 mg vericiguat	2x	6.7x	24x	54x
$AUC_{0\text{-last}}$ day 387(µg.hr/ml) M1 (BAY1222707)	416	1140	4270	9750
Multiple of human AUC 10 mg M1	<0.25	<0.25	<0.25	0.26x
Female mice				
Dose mg/kg/day	6	20	60	250
$AUC_{0\text{-last}}$ day 359(µg.hr/ml) Vericiguat (BAY1021189)	17600	59700	180000	522000
Multiple of human AUC 10 mg vericiguat	2.4x	8x	25x	71x
$AUC_{0\text{-last}}$ day 359(µg.hr/ml) M1 (BAY1222707)	546	2170	5590	22700
Multiple of human AUC 10 mg M1	<0.25	<0.25	<0.25	0.6x

Healthy human volunteers (mean values)	Cmax µg/L	AUCτ
Vericiguat 10 mg steady state	398	7320 µg hr/L
M1	1610	38,000µg hr/L

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9 Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

The study used doses of 0, 5, 15, and 50 mg/kg/day and achieved a maximally tolerated dose as the highest dose administered (50 mg/kg) produced clinical signs of piloerection as well as an increase in weight gain over the control group. While there was no overall effect on fertility, a dose-related decrease in estrus cycles was apparent with a decrease of 24% in the 50 mg/kg/day group. This was concurrent with a 24% increased time to insemination in the same dose group. There were no apparent effects on pre- or post-implantation loss nor on viability of embryos. Toxicokinetics were not conducted for this study.

Embryo-fetal Development

Rabbits

A maximally tolerated dose was achieved in this study as both the mid-dose and high dose groups had unscheduled mortality. Eight high dose females were euthanized due to abortion from GD24 onwards. The majority of animals had some weight loss, and decreased or altered fecal appearance. The mid-dose showed lesser toxicity as 3 females were euthanized due to abortion. The early decedent animals in both these groups showed weight loss, changes in feces, discolored urination, and discoloration of the liver.

There were no effects on the general parameters of implantations, corpora lutea, or preimplantation loss. Postimplantation loss in the highest dose group was statistically significantly ($p<0.01$) increased over the control group. The rate of spontaneous abortion increased with increasing dose as summarized in the table below. A slight, non-statistically significant increase in ovarian cysts was reported. This was also noted in the 2-year rodent carcinogenicity studies. Both the incidence of ovarian cysts and the fetal malformations are summarized in the reviewer's table below. (Ovarian cysts were reported also in the rat 2-year carcinogenicity study). The lowest dose of 0.75 mg/kg/day was the NOAEL for both maternal and developmental effects.

Summary of malformations

rabbit Dose mg/kg	0	0.75	2.5	7.5
Cardiac ventricular septal defect	3(3)	0	2(2)	1
Malformation of heart and major vessels, cardiac septal defect, truncus arteriosus communis	0	0	2(2)	1
Right ventricle enlarged			1	
Ovarian cysts Euthanized due to abortion # of Females with viable fetuses of those with implantation sites	1 0 17	1 0 18	2 3 17	3 8 10**

Numbers in parentheses( ) are numbers of affected litters. ** = $p<0.01$
A total of 6 drug-treated rabbit litters had pups affected with cardiac defects

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Summary of rabbit toxicokinetics

Daily dose (mg/kg)	0(control)	0.75	2.5	7.5
Toxicokinetics GD20				
# of females	3	3	3	3
AUC_{0-24} (µg hr/L)	NA	5590	2490	105000
C_{max} (µg/L)	NA	509	2180	7590
T_{max} (hr)	NA	2.00	4.00	4.82
Mortality (number of females)				
Found dead	0	1	0	0

Rats

A maximally tolerated dose was apparent in this study due to the dose-related decrease in body weight gain. The high dose group receiving 50 mg/kg/day gained on average 36% ($p<0.01$) less than the control group. A NOAEL for maternal effects was 5 mg/kg/day. The incidences of malformations fell within historical control ranges with no convincing trends suggestive of a drug-related effect. A NOAEL for developmental effects was 50 mg/kg/day.

Summary of rat toxicokinetics

Daily dose (mg/kg)	5	15	50
Toxicokinetics GD17			
# of females	4	4	4
AUC_{0-24} (µg hr/L)	28600	67100	240000
C_{max} (µg/L)	2700	5490	17700
T_{max} (hr)	7.00	3.48	5.28

Pre- and Post-natal Development

There were developmental effects identified in both sexes of pups. No toxicokinetics were provided with the study so it is not possible to compare to human exposure based on AUC values. Samples of milk were not analyzed for secretion or concentration of drug-related material.
The LOAEL for delayed vaginal opening was 7.5 mg/kg/day, the lowest dose tested. The delays At the lowest dose were significant at $p<0.05$ and at the highest dose were significant at $p< 0.001$.
The NOAEL for delayed balanopreputial separation was 30 mg/kg/day, the highest dose tested. This groups showed a mean delay of 6 days($p<0.001$) compared to the control group. The safety margin based on body surface area is shown in the table below.

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Other developmental markers showed dose-related delays:

	% of pups showing the landmark			
	control	7.5mg/kg	15mg/kg	30 mg/kg
Positive surface righting on PND1	80%	70	70	53
Pinna unfolding on LD2 Historical control range: 35-69% LD2	86%	71	59	43
Exposure based on mg/m2				
Rat dose (mg/m2;km = 6)	na	45	90	180
MRHD of 10 mg in mg/m2 (km =37)				
50 kg human	7.4 mg/m^2	6-fold		24-fold
65 kg human	5.7 mg/m^2	8-fold		32-fold

From the data provided, it is not possible to distinguish whether the effects on various developmental landmarks, including reaching sexual maturity, were primary effects on endocrine axes, or were secondary to maternal nursing behavior or pup locomotion and nursing.

Juvenile Animal Studies

A pilot study in juvenile rats used doses of 0, 3, 10 and 30 mg/kg/day from post-natal day 10 to post-natal day 29. The methods were not clearly described. None of the animals receiving 30 mg/kg/day survived to scheduled euthanasia. The cause of death is unclear. A very mild but regenerative anemia was apparent at the 10 mg/kg dose. The text of the report stated that due to the younger age at necropsy, rats of the 30 mg/kg group showed juvenile bone histopathology that was described as having increased remodeling and cellularity compared to pups euthanized at scheduled study termination.

The sponsor provided a 13-week repeat dose juvenile animal toxicology study with an interim analysis at 4 weeks and two drug-free recovery groups, one after 4 weeks of dosing and one after 13 weeks of dosing. A striking result was the animals receiving 10 mg//kg in the 13-week cohort showed numerous clinical signs including premature death associated with necrotizing enteritis. Cannibalism and autolysis made it impossible to determine cause of death for 7 out of 16 deaths. Survivors in the 10 mg/kg cohort also showed clinical signs that were not apparent in the 4-week cohort of the same dose. These signs included emaciation, piloerection, salivation, audible breathing sounds (dyspnea?), and dysmetria (high stepping gait). Alterations in gait have been noted in adult rats in both the single dose safety pharmacology and repeat dose adult toxicology, reported at higher plasma exposures. The respiratory signs have also been reported in adult rats in repeat dose toxicology studies, also at higher exposure levels. The sponsor did not address the differences in sensitivity between the 4-week and 13-week results except to suggest that the one group of rats was genetically more susceptible.

Thickened growth plates and hyperostosis have been reported at doses of 30 mg/kg or greater in the standard toxicology studies (AUC_{0-24} 151914 µg.hr/l) in adult rats and the pilot JAS (AUC_{0-last} 71100 µg.hr/l), no effects on either bone histopathology or growth were reported in the 13-week JAS study, in which 10 mg/kg was the highest dose studied. Neither sex of pup showed a

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delay in reaching developmental landmarks, different from the pre- and post-natal development study (Segment III). However, histologic evaluation of the reproductive organs of the drug-treated rats showed "immaturity" while none of the control animals received a similar designation. This became the subject of an Information Request that was presented several times to the sponsor. After the third request, the sponsor addressed the question of the immaturity by saying in essence that the complexity of the study design and the manner of reporting left the data open to misinterpretation. The hypothesis of genetic differences in the groups of animals was proposed but without supporting information, e.g., the breeding animals producing the test animals were different.

The plasma levels of BAY1021189 showed a non-linear increase with increasing dose and a decrease in exposure over the duration of the study. The plasma exposure to test article in the juvenile rats was similar to adult exposure reported for the 6-month repeat dose toxicology. Over time, the exposure in juvenile rats decreased while the exposure in adult rats increased.

Reviewer's summary of plasma exposure in juvenile rats definitive study						
	Males dose (mg/kg)			Females dose (mg/kg)		
	1	3	10	1	3	10
Day 1 $AUC_{(0\text{-tlast})}$ (µg.hr/L)	8430	19700	34800	8150	16200	35800
Day 72 $AUC_{(0\text{-tlast})}$ (µg hr/L)	1790	4930	14400	1680	4670	10800
[redacted]						
Examples of adult plasma exposure at similar doses						
		3	10		3	10
6-month rat study day 1 $AUC_{0\text{-tlast}}$ µg h/L		8390	29000		13200	44500
6-month rat study day 149 $AUC_{0\text{-tlast}}$ µg h/L		13800	45000		16800	62600

Reviewer's Summary of Drug Exposure in juvenile pilot study						
	males			females		
Dose mg/kg	3	10	30	3	10	30
Day 1: $AUC_{0\text{-last}}$ (µg hr/l)	18000	42700	64000	18200	41900	71100
Day 15: $AUC_{0\text{-last}}$ (µg hr/l)	5210	14000	No survivors	6360	17500	No survivors
Day 29: $AUC_{0\text{-last}}$ (µg hr/l)	3510	18800	No survivors	7780	31200	No survivors

10 Special Toxicology Studies

Phototoxicity

Phototoxicity was assessed in vitro in 3T3.A31 mouse fibroblasts with Neutral Red uptake for viability assessment. BAY1021189 was tested at concentrations up to the limit of solubility in phosphate buffered saline. Under the conditions of the study, BAY1021189 showed a photoirritation factor of 1, less than the OECD benchmark of 5 as indicative of phototoxic potential.

Local Tolerance

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Local tolerance was assessed as part of the repeat dose toxicology studies. As this is an orally administered drug, the evaluation consisted of the histopathological examination of the gastrointestinal tract. The histopathological examination indicated effects that may reasonably be associated with a smooth muscle relaxant rather than indications of local intolerance.

Antigenicity/Immunogenicity/Immunotoxicity
No dedicated antigenicity or immunogenicity evaluations were conducted. The 28-day repeat dose rat study included endpoints of splenic cell counts and splenic cell subpopulations. As there were no indicators of effects on the immune system, no further specific evaluation was conducted.

11 Integrated Summary and Safety Evaluation

The sponsor has conducted the nonclinical studies recommended under the ICH guidelines to support chronic use in humans. This includes safety pharmacology, off-target assessment, repeat dose toxicology studies up to 6 months duration in rats, up to 39 weeks in dogs, 2-year rodent carcinogenicity studies, genetic toxicology, developmental and reproductive toxicology and juvenile animal studies. The pivotal studies were conducted in accordance with GLP guidelines and used the oral route of administration, consistent with the clinical route of administration.

The primary effect of vericiguat is smooth muscle relaxation. This produces vasodilation, reduced vascular tone, and reduced cardiac afterload, thus hypothetically slowing the pathologic processes of heart failure. Systolic, diastolic, and mean arterial blood pressure are consistently lowered. Secondary effects include altered gastrointestinal motility and bone metabolism. The bone effects were most apparent in the shorter term studies using adolescent rats and included hypertrophy of the growth plate, hyperostosis, and remodeling of metaphyseal and diaphyseal bone. These effects were not reported in the definitive juvenile animal study or the 2-year carcinogenicity studies. Nor were effects reported for the repeat dose dog toxicology studies. Soluble guanylate cyclase was identified as a significant factor in the regulation of osteoblast metabolism some decades ago (Fukushima and Gay, 1991). There is a dichotomy of views on the bone effects from sGC modulation. Some have proposed this as a target treatment for osteoporosis based on ex vivo work and a less than well-regarded animal model of osteoporosis (Joshua et. al. 2014). Homer et. al (2015) administered sGC compounds to several different age groups of rats, ranging from 7 weeks old to 42 weeks (aged). In each of these studies, the rats received drug orally, once a day for 7 days, then were euthanized 24 hours after the last dose. Several heme-dependent (HD-sGC) and heme-independent (HI-sGC) compounds were assessed. The incidence and severity of bone morphologic changes were dose-dependent and similar for both classes of sGC compounds. The bone changes included increased numbers of osteoclasts, osteoclastic bone resorption and porosity in tibia and femur, and variable formation of new

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woven bone. When spine and head were also examined, changes could also be found in the vertebral bodies, the mandible, palatine bone, and at various sites of muscle attachment to the skull. The bone changes in the aged rats were reported as similar to those of the younger rats, suggesting that these changes may be relevant to an older population. It is unclear how the variability of the plasma drug concentrations might affect the bone morphological changes. However, the bone effects reported by Homer et al (2015) are consistent with effects reported at all ages during the nonclinical development of riociguat. The publications and work by several independent investigators supports a class effect for sGC stimulators to modulate bone metabolism.

Early in development, urinary crystals were reported for both rats and dogs. These were insoluble crystals described as resembling sea urchins. There was no mention of this in the studies conducted later in development, that is, the long-term toxicology studies. It is not clear what the source of the crystals was or how the matter was resolved.

The cardiovascular safety pharmacology suggested effects on several ion channels. In vitro, the parent drug achieved 50% inhibition of the hERG channel at 10µM. Conscious telemetered Beagles showed a dose-related prolongation of the PR interval by approximately 16% of baseline along with a slight (2%) change in duration of the QRS interval. No NOAEL was identified. There also appeared to be a rebound effect of increased blood pressure starting approximately 14 hours after administration of the drug.

The embryo-fetal development studies suggested that vericiguat is teratogenic with respect to formation of the heart and great vessels. This was demonstrated in the rabbit study in which 6 different drug-treated litters had pups with cardiac defects. The NOAEL was 0.75 mg/kg.

There were developmental effects identified in both sexes of pups with a LOAEL of 7.5 mg/kg/day. No toxicokinetics were provided with the study so it is not possible to compare exposure of the pups based on AUC values. Samples of milk were not analyzed for secretion or concentration of drug-related material. It is not possible to distinguish whether the effects on various developmental landmarks, including reaching sexual maturity, were primary effects on endocrine axes, or were secondary to maternal nursing behavior or pup locomotion and nursing. The juvenile animal studies that have been provided for vericiguat indicate an increased sensitivity to the drug when dosed directly. This increased sensitivity was manifested primarily as necrotizing enteritis

Vericiguat did not demonstrate genotoxic, phototoxic, or carcinogenic potential in the respective studies. Increasing duration of the repeat dose toxicology did not indicate new toxicities or new target organs. Consistent targets throughout the studies were the liver, kidneys, and adrenals. Inconsistent, somewhat inconclusive signals for endocrine effects were apparent throughout the nonclinical studies. This may be related to the affinity of the parent drug and M1 metabolite for the dopamine transporter.

The major circulating metabolite, M1, an N-glucuronide referred to as BAY1222707, has also been evaluated as far as in vitro pharmacology. This metabolite constituted approximately 70%

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of circulating drug-related material in humans and approximately 10% in the nonclinical species. As this is an N-glucuronide rather than an acyl-glucuronide, there is less likelihood of significant pharmacologic or toxicologic activity although M1 has some similarity to the parent drug in off-target activity.

12 References

Fukushima O and CV Gay. Ultrastructural localization of guanylate cyclase in bone cells. J Histochem and Cytochem 39(4), 1991.

Homer BL, et. al. Oral administration of soluble guanylate cyclase agonists to rats results in osteoclastic bone resorption and remodeling with new bone formation in the appendicular and axial skeleton. Tox Path 43:411-423, 2015.

Joshua J, et. al. Soluble guanylate cyclase as a novel treatment target for osteoporosis. Endocrinology 155:4720-4730, 2014.

13 Appendix/Attachments

Summary of Reviews for IND116743

Application	Reviewer	SDN	Date in DARRTs	Notes
116743	Hausner	002	8/30/2013	Pharmacology, PK (beagles, rats), 4-week tox, genetic tox, in vitro photoxicity
		013	12/18/2013	QWBA, 13-week tox in rats and dogs
		028	9/22/2014	39-week toxicology in dogs
		039	6/5/2015	2 – and 13-week study in Long Evans rats for melanin binding
		041	7/6/2015	Memo regarding the information requested pertaining to melanin findings
		051, 052	1/21/2016	2week mice, 13week mouse dietary, 13 week rat study (Carcinogenicity background), M1 summary

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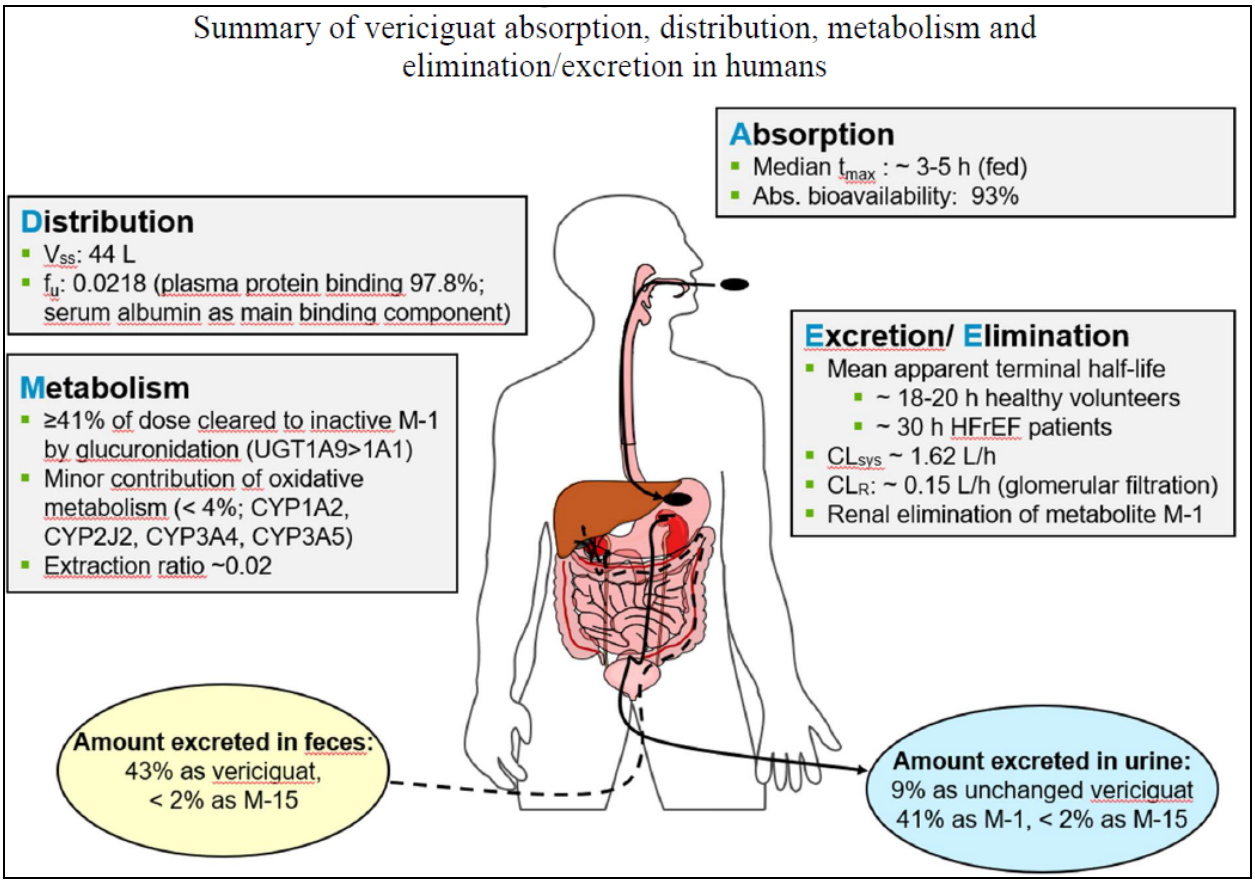
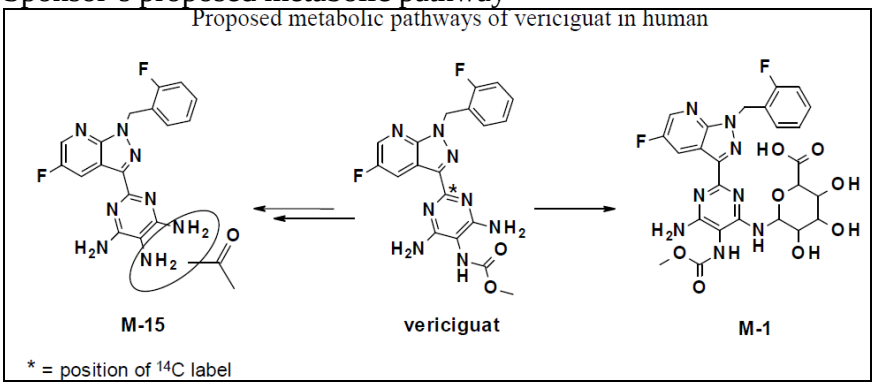
		053, 058	2/26/2016	6-month rat(with micronucleus), Pilot JAS, Fertility, SegII in rats and rabbits, impurities, CV Safety Pharm (pig)
	Seifried	Final Exec CAC minutes	3/9/2016	Meeting date 1/12/2016. Review of study protocols
	Hausner	063	4/19/2016	Urinary crystals
		070	6/3/2016	Further discussion of urinary crystals
		130	4/16/2018	Memo re Sponsor's response for Exec CAC response for early termination of study
		143	9/13/2018	4 week and 13 week JAS
		182		
		memo	5/13/2019	Memo regarding IR for JAS studies.
		memo	12/9/2019	Memo regarding third attempt at the same IR for JAS
	Malick	203,204, 206	7/6/2020	Statistical review for carcinogenicity studies
	Hausner	203,204, 206	7/1/2020	Review of carcinogenicity studies
	Aziz	FRM-minutes	7/1/2020	Exec CAC minutes of final study reports
	Hausner	0173	6/22/2020	Pre- and post-natal development

Sponsor's Depiction of Human ADME

Reference ID: 4679731



Sponsor's proposed metabolic pathway



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/s/

ELIZABETH A HAUSNER
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10/02/2020 08:49:08 AM

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number:	IND 116743
Drug Name:	Vericiguat (BAY 1021189)
Indication(s):	Treatment of chronic cardiovascular diseases.
Studies	Two Year Oral Gavage Carcinogenicity Study in Rats and Two Year Oral Dietary Carcinogenicity Study in Mice.
Applicant:	Sponsor: Merck and Bayer Test facility: (b) (4)
Documents Reviewed:	Electronic submission, dated: March 26, 2020 via SN0203 Electronic data submitted on May 12, 2020 via SN0203.
Review Priority:	Priority
Biometrics Division:	Division of Biometrics -VI
Statistical Reviewer:	Malick Mbodj, Ph.D.
Secondary Reviewer:	Hepei Chen
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Cardiology, Hematology, Endocrinology, and Nephrology
Reviewing Pharmacologist:	Elizabeth Hausner, PhD
Project Manager:	Alexis T. Childers, RAC, CQIA
Keywords:	Carcinogenicity, Dose response

Reference ID: 4736022

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1. Background

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in RccHan:Wist rats and one in Crl:CD1(ICR) mice. These studies were intended to assess the carcinogenic potential of BAY 1021189 in rats and mice when administered orally, by gavage and by dietary, at appropriate drug levels for about 104 weeks in rats and in mice, respectively. Results of this review have been discussed with the reviewing pharmacologist Dr. Hausner.

In this review, the phrase "dose response relationship" (trend) refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Rat Study

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups, one water control group, and one vehicle control group. Three hundred RccHan:Wist rats of each sex were assigned to five groups: three treated groups, one water control group, and one vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 60 animals, as indicated in Table 1. The dose levels for the three treated groups were 2, 6, and 20 mg/kg/day for both males and females, for up to 104 weeks. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The vehicle control group received the vehicle (Ethanol/Kolliphor HS 15®/purified water or water for irrigation (10/40/50 v/v/v)), administered orally by gavage for about 104 weeks in the same manner as the treated groups. The water control item was purified water or water for irrigation

Table 1: Experimental Design in Rat Study

Group Name	Group N0.	Dose Level (mg/kg/day)		Number of Animal	
		Male	Female	Males	Females
Vehicle Control	1	0	0	60	60
Water Control	2	0	0	60	60
Low	3	2	2	60	60
Medium	4	6	6	60	60
High	5	20	20	60	60

During the study period all animals were observed for general health/mortality and moribundity twice daily (the beginning and end of each working day), abnormal findings were recorded throughout the study. Cage side observations were conducted for each carcinogenicity animal once daily during the dosing phase, except on days when detailed observations were conducted. Detailed observations were conducted for each carcinogenicity animal at least once prior to dosing on Day 1, and weekly thereafter throughout the dosing phase. Detailed examinations for palpable masses were done weekly, the time of onset, location, size, appearance, and progression of each grossly visible or palpable mass, observed in carcinogenicity rats, was recorded weekly. Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively will be euthanized. Observations will include, but will not be limited to, evaluation for reaction to treatment. Histopathological examinations were performed on all animals found dead or killed moribund or sacrificed at the end of the experiment. Individual body weights of all animals were recorded on Day 1 of the predose phase, once daily from Days 1 (before dose) to 14 of the dosing phase, once weekly from Day 15 (before dose) to Week 16, once every 4 weeks from the start of Week 17, once weekly from the start of Week 69, during Week 105, and before each necropsy.

2.1. Sponsor's analyses

2.1.1. Survival analysis

In the sponsor's analysis, the tests for survival comparisons were performed with a two-sided risk for increasing and decreasing mortality with dose. Tests were performed for dose response (vehicle control and dosed groups only), and for the water control and each treated group against the vehicle control group using Kaplan-Meier product-limit estimates, along with log-rank and Wilcoxon tests. These were performed using the LIFETEST procedure in SAS. The time to death or sacrifice (in weeks) was the dependent variable. Treatment group was included as the strata

Any animal with accidental injury that causes its death, or its unscheduled sacrifice was censored in the estimation. In addition, all animals still alive at the end of the experimental period were censored at the following day. Results of all pair-wise comparisons are reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

Sponsor's findings:

Sponsor's analysis showed the numbers of rats surviving to their terminal necropsy were 35 (58%), 37 (62%), 37 (62%), 36 (60%), and 38 (63%) in the vehicle control group, water control, low, medium, and high dose groups, in male rats, respectively, and 39 (65%), 36 (60%), 40 (67%), 37 (62%), and 35 (58%) in vehicle control, water control, low, medium, and high dose groups, in female rats, respectively. The sponsor's report concluded that there were no statistically significant findings in survival rate in either sex of rats.

2.1.2. Tumor data analysis

In the sponsor's analysis, tests to compare tumor incidence were performed, with a one-sided risk for increasing incidence with dose. Tests were performed for dose response (vehicle control and dosed groups only) and for the water control and each dosed group against the vehicle control group. Occult or non-palpable tumors were analyzed by the IARC asymptotic fixed interval-based prevalence test (Peto et al., 1980). The cut-off points for the interval-based test were Weeks 0 to 52, 53 to 78, 79 to 92, 93 through before the terminal sacrifice, and at terminal sacrifice. Actual dose levels were used as the scores. Fatal and non-fatal tumors were analyzed together, with separate stratum for each. Tumors of uncertain context of observation were included in the analysis as non-fatal. The test was implemented using PROC MULTTEST in the SAS system (SAS, 2008). In the case of sparse tables (<10 total tumor bearing animals in the groups analyzed for the trend or pairwise test), the exact form of the test was used. Otherwise, the asymptotic version of the test was used. The dose response will be performed using a Cochran-Armitage test for trend Armitage, 1955). The pairwise comparisons of groups will be performed using Fisher's exact test (Thakur et al., 1985). All tests will be performed with two-sided risk.

Incidences of multiple-organ and combined neoplastic findings, such as hemangioma, fibrosarcoma, and endometrial stromal polyp were counted by animal, not by tissue type. Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded in the data and were not assigned based on the day/week of necropsy.

Adjustment for the multiplicity:

Unadjusted P-values were reported for tumors. Indications of a possible treatment effect were assessed on the basis of rare or common tumor type, in line with the current FDA guidelines (Food and Drug Administration, 2001). Briefly, as to trend analysis, common and rare tumors were tested at 0.005 and 0.025 significance levels, respectively. As to pairwise comparisons, common and rare tumors were tested at 0.01 and 0.05 significance levels, respectively. Site-specific background historical control database was used to determine whether the tumors should be designated as rare or common.

Sponsor's findings:

The sponsor's analysis showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased BAY 1021189 dose. The pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidences in BAY 1021189 treated groups, when compare to the vehicle control group in either male or female rats.

2.2 Reviewer's analyses

To verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed the survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on March 26, 2020 via SN0203.

2.2.1 Survival analysis

In the reviewer's analysis, intercurrent mortality data were analyzed using the Kaplan-Meier product limit method. The Kaplan-Meier's curves were presented graphically for male and female rats separately. The dose response relationship and homogeneity of survival distributions were tested for the treatment groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female rats, respectively.

Reviewer's findings:

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 35 (58%), 37 (62%), 37 (62%), 36 (60%), and 38 (63%) in the vehicle control group, water control, low, medium, and high dose groups, in male rats, respectively, and 39 (65%), 36 (60%), 40 (67%), 37 (62%), and 35 (58%) in vehicle control, water control, low, medium, and high dose groups, in female rats, respectively. This reviewer's analysis showed no statistically significant increase in mortality across the vehicle control group and the three treated groups in either sex of rats. The pairwise comparisons showed no statistically significant increase or decrease in mortality between each of the treated groups and the vehicle control group in either sex of rats.

2.2.2. Tumor data analysis

In the reviewer's analysis, the tumor data were analyzed for dose response relationship across vehicle control group and the treated groups, as well as the pairwise comparisons of vehicle control group with each of the treated groups using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method, an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice with development of the tumor type being tested gets a score of s_h =1. An animal that

dies at Week w_h without development of the given tumor type before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k$ <1. The adjusted group size is defined as Σs_h. As an interpretation, an animal with score s_h =1 can be considered as a whole animal, while an animal with score s_h <1 can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal develops the given tumor being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise comparison) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104-week standard rat and mouse studies, a value of k=3 is suggested in the literature [Gebregziabher and Hoel (2009), Moon et al. (2003), Portier, et al. (1986)]. Hence, this reviewer used k=3 for the analysis of the data. Based on the intent to treat (ITT) principle Wmax was considered as 105 for both male and female rats.

For the calculation of p-values, if there were less than 10 tumor bearing animals across all treatment groups for a given tumor type, the exact tests based on the discrete permutation distribution were used, with dose levels (0, 0, 2, 6, and 20 for both male rats and female rats) as scores, and asymptotic tests were used for tumor types with higher incidences. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male rats and female rats, respectively.

Multiple testing adjustments:

Following the FDA draft guidance for the carcinogenicity study design and data analysis 2001, for the two-year rat study this reviewer used significance levels of 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

A tumor is defined as a rare tumor if the published spontaneous rate or the spontaneous rate of the vehicle control of the tumor is less than 1%, and a common tumor is defined as one with tumor rate greater than or equal to 1%.

Reviewer's findings:

The tumor types with p-values less than 0.05 for dose response relationship and/or pairwise comparisons of vehicle control and treated groups are reported in Table 2.

Table 2: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons
Treated Groups and Control Group in Rats

Sex	Organ Name	Tumor Name	0 mg Cont (N=60) P - Trend	0mg Water Cont (N=60)	2 mg Low (N=60) P - C vs. L	6 mg Med (N=60) P - C vs. M	20 mg High (N=60) P - C vs. H
Male	Adrenal	B-Phaeochromocytoma, Benign	4/60 (51) 0.0183@@	2/60 (53) NC	4/60 (52) 0.6532	6/60 (53) 0.3955	10/60 (50) 0.0686
		B-Phaeochromocytoma, Benign / M-Phaeochromocytoma Malignant	4/60 (51) 0.0210@@	3/60 (53) NC	4/60 (52) 0.6532	7/60 (53) 0.2856	10/60 (50) 0.0686
	Testis	B-Adenoma, Leydig Cell	2/60 (51) 0.0076@@	0/60 (53) NC	1/60 (52) 0.8822	0/60 (52) 1.0000	6/60 (50) 0.1281

@@: not Statistically significant at 0.005 for common tumor in dose response relationship

Following the multiple testing adjustment method described above, this reviewer's analysis showed no tumor types with a statistically significant positive dose response relationship in tumor incidences with increased BAY 1021189dose. The pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidences in BAY 1021189 treated groups, when compare to the vehicle control group in either male or female rats.

3. Mouse Study

Two separate experiments were conducted, one in male mice and one in female mice. In each of these two experiments there were four treated groups, and one vehicle control group. three hundred Crl:CD1(ICR) mice of each sex were assigned randomly to one of the five groups by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 60 animals. The dose levels for the four treated groups were 5, 15, 50, and 150 mg/kg/day for males and 6, 20, 60, and 250 mg/kg/day for females, for up to 104 weeks, as indicated in Table 3. In this review, these dose groups would be referred to as the low, medium, medium-high, and high dose group, respectively. Animals were exposed to the test item via the diet daily for up to 104 weeks. The control article (vehicle) was 5LF2 EU Rodent Diet, were administered in the same manner as the treated groups. The female mice were scheduled for early terminal sacrifice in week 93 and 94 due to the vehicle control group having less than 15 surviving animals.

Table 3: Experimental Design in Mouse Study

Group Name	Group N0.	Dose Level (mg/kg/day)		Number of Animal	
		Male	Female	Males	Females
Vehicle Control	1	0	0	60	60
Low	2	5	6	60	60
Medium	3	15	20	60	60
Medium-High	4	50	60	60	60
High	5	150	250	60	60

During the study period all animals were observed for general health/mortality and moribundity twice daily (the beginning and end of each working day), abnormal findings were recorded throughout the

study. Cage side observations were conducted for each carcinogenicity animal once daily during the dosing phase, except on days when detailed observations were conducted. Detailed observations were conducted for each carcinogenicity animal at least once prior to dosing on Day 1, and weekly thereafter throughout the dosing phase. Detailed examinations for palpable masses were done weekly, the time of onset, location, size, appearance, and progression of each grossly visible or palpable mass, observed in carcinogenicity rats, was recorded weekly. Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively will be euthanized. Observations will include, but will not be limited to, evaluation for reaction to treatment. Histopathological examinations were performed on all animals found dead or killed moribund or sacrificed at the end of the experiment. Individual body weights of all animals were recorded on Day 1 of the predose phase, daily on Days 1 through 14 of the dosing phase, once weekly from Day 15 until Week 29 of the dosing phase, once every 4 weeks during Weeks 29 through 68 of the dosing phase, once weekly during Weeks 69 through 105 of the dosing phase, and before each necropsy.

3.1. Sponsor's analyses

3.1.1 Survival analysis

The sponsor used similar methodologies to analyze the mouse survival data as those used to analyze the rat survival data.

Sponsor’s findings:

Sponsor’s analysis showed the numbers of mice surviving to their terminal necropsy were 35 (58%), 35 (58%), 24 (40%), 27 (45%), and 28 (47%), in vehicle control, low, medium, medium-high, and high dose groups in male mice, respectively, and 15 (25%), 23 (38%), 29 (48%), 37 (62%), and 31 (52%), in female mice, respectively. The sponsor’s report concluded that there were no statistically significant findings in survival rate in male mice. However, in female mice, the pairwise comparison showed a statistically significant decreased mortality in medium , medium-high and high dose group when compared to the vehicle control group with p-value = 0.0166, 0.0002, and p-value = 0.0029 using log-rank test respectively, and p-value = 0.0404, 0.0025, and p-value = 0.0075 using Wilcoxon test respectively

3.1.2 Tumor data analysis

The sponsor used similar methodologies to analyze the mouse tumor data as those used to analyze the rat tumor data.

The analysis of tumors was based on the following fixed time intervals: Weeks 1 to 52, 53 to 78, 79 to 92, 93 to before terminal sacrifice, and the terminal sacrifice for male mice and Weeks 1 to 52, 53 to 78, 79 to before terminal sacrifice, and the terminal sacrifice for female mice. The actual dose levels were used as the scores.

Multiple testing adjustment:

For multiplicity testing adjustment, the sponsor used similar testing adjustment as those used to analyze the rat tumor data, in line with the current FDA draft guidelines (Food and Drug Administration, 2001).

Sponsor’s findings:

The sponsor's analysis showed no tumor types with a statistically significant positive dose response relationship in tumor incidences with increased BAY 1021189 dose. The pairwise comparisons showed no tumor types with a statistically significant increase in tumor incidences in BAY 1021189 treated groups, when compare to the vehicle control group in either male or female mice.

3.2 Reviewer's analyses

Similar to the rat study, this reviewer independently performed the survival and tumor data analyses of the mouse study. For the analysis of the survival data and the tumor data of the mouse study, this reviewer used similar methodologies that were used for the analyses of the survival and tumor data of the rat study. Data used in this reviewer's analyses were provided by the sponsor electronically.

3.2.1 Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for male and female mice, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for male and female mice, respectively. Results for test of dose response relationship and homogeneity of survivals among treatment groups are given in Tables 5A and 5B in the appendix for male and female mice, respectively.

Reviewer's findings:

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 35 (58%), 35 (58%), 24 (40%), 27 (45%), and 28 (47%), in vehicle control, low, medium, medium-high, and high dose groups in male mice, respectively, and 15 (25%), 23 (38%), 29 (48%), 37 (62%), and 31 (52%), in female mice, respectively. This reviewer's analysis showed that there were no statistically significant findings in survival rate in male mice. However, this reviewer's analysis showed a statistically significant dose response relationship in the mortality of female mice with p-value = 0.0458. The pairwise comparison showed a statistically significant decreased mortality in medium, medium-high and high dose group when compared to the vehicle control group in female mice with p-value = 0.0187, p-value = 0.0002, and p-value = 0.0036, respectively.

3.2.2 Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and the pairwise comparisons of vehicle control and treated groups are given in Table 6A and 6B in the appendix for male and female mice, respectively.

Multiple testing adjustment:

Also following the FDA draft guidance for the carcinogenicity study design and data analysis 2001, for the two-year mouse study this reviewer used significance levels of 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

Reviewer's findings:

The tumor types with p-values less than 0.05 for dose response relationship and/or pairwise comparisons of vehicle control and treated groups are reported in Table 4.

Table 4: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons
Treated Groups and Control Group in Mice

Sex	Organ Name	Tumor Name	0 mg Cont (N=60) P - Trend	5 mg Low (N=60) P - VC vs. L	15 mg Med (N=60) P - VC vs. M	50 mg Med-High (N=60) P - VC vs. MH	150 mg High (N=60) P - VC vs. H
Male	Haemolympho-Reticular System	M-Malignant Lymphoma-Lymphoblastic	0/60 (49) 0.0290@@	0/60 (48) NC	0/60 (44) NC	1/60 (45) 0.4787	2/60 (45) 0.2265
	Liver	B-Hepatocellular Adenoma/ M-Hepatocellular Carcinoma	8/60 (50) 0.8439	15/60 (50) 0.0765	16/60 (49) 0.0442@	8/60 (45) 0.5159	8/60 (44) 0.4961

Sex	Organ Name	Tumor Name	0 mg Cont (N=60) P - Trend	6 mg Low (N=60) P - VC vs. L	20 mg Med (N=60) P - VC vs. M	60 mg Med-High (N=60) P - VC vs. MH	250 mg High (N=60) P - VC vs. H
Female	Harderian Gland	B-Adenoma	2/60 (31) 0.9974	3/60 (35) 0.5585	10/60 (37) 0.0261@	0/60 (34) 1.0000	0/60 (35) 1.0000
	Ovary	B-Tubulostromal Adenoma	0/60 (30) 0.0366@@	0/59 (33) NC	0/59 (33) NC	1/60 (35) 0.5385	2/60 (35) 0.2861
	Uterus	B-Polyp, Endometrial Stromal	1/60 (30) 0.6025	8/60 (36) 0.0271@	8/60 (36) 0.0271@	3/60 (36) 0.3789	5/60 (37) 0.1543

@@: not Statistically significant at levels of 0.005 and 0.025 for common and rare tumors respectively in dose response relationship
@: not Statistically significant at 0.01 for common tumor in pairwise comparison

Following the multiple testing adjustment method described above, this reviewer's analyses showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased BAY 1021189 dose in either sex of mice. The pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidences in BAY 1021189 treated groups, when compare to the vehicle control group in either male or female mice.

4. Summary

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in RccHan:Wist rats and one in Crl:CD1(ICR) mice. These studies were intended to assess the carcinogenic potential of BAY 1021189 in rats and mice when administered orally, by gavage and by dietary, at appropriate drug levels for about 104 weeks in rats and in mice, respectively.

Rat Study:

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups, one water control group, and one vehicle control group. Three hundred RccHan:Wist rats of each sex were assigned to five groups: three treated groups, one water control group, and one vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 60 animals, as indicated in Table 1. The dose levels for the

three treated groups were 2, 6, and 20 mg/kg/day for both males and females, for up to 104 weeks. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The vehicle control group received the vehicle (Ethanol/Kolliphor HS 15®/purified water or water for irrigation (10/40/50 v/v/v)), administered orally by gavage for about 104 weeks in the same manner as the treated groups.

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 35 (58%), 37 (62%), 37 (62%), 36 (60%), and 38 (63%) in the vehicle control group, water control, low, medium, and high dose groups, in male rats, respectively, and 39 (65%), 36 (60%), 40 (67%), 37 (62%), and 35 (58%) in vehicle control, water control, low, medium, and high dose groups, in female rats, respectively. This reviewer's analysis showed no statistically significant increase in mortality across the vehicle control group and the three treated groups in either sex of rats. The pairwise comparisons showed no statistically significant increase or decrease in mortality between each of the treated groups and the vehicle control group in either sex of rats.

For tumor data, this reviewer's analysis showed no tumor types with a statistically significant positive dose response relationship in tumor incidences with increased BAY 1021189 dose. The pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidences in BAY 1021189 treated groups, when compare to the vehicle control group in either male or female rats.

Mouse Study:

Two separate experiments were conducted, one in male mice and one in female mice. In each of these two experiments there were four treated groups, and one vehicle control group. three hundred Crl:CD1(ICR) mice of each sex were assigned randomly to one of the five groups by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 60 animals. The dose levels for the four treated groups were 5, 15, 50, and 150 mg/kg/day for males and 6, 20, 60, and 250 mg/kg/day for females, for up to 104 weeks, as indicated in Table 3. In this review, these dose groups would be referred to as the low, medium, medium-high, and high dose group, respectively. Animals were exposed to the test item via the diet daily for up to 104 weeks. The control article (vehicle) was 5LF2 EU Rodent Diet, were administered in the same manner as the treated groups. The female mice were scheduled for early terminal sacrifice in week 93 and 94 due to the vehicle control group having less than 15 surviving animals.

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 35 (58%), 35 (58%), 24 (40%), 27 (45%), and 28 (47%), in vehicle control, low, medium, medium-high, and high dose groups in male mice, respectively, and 15 (25%), 23 (38%), 29 (48%), 37 (62%), and 31 (52%), in female mice, respectively. This reviewer's analysis showed that there were no statistically significant findings in survival rate in male mice. However, this reviewer's analysis showed a statistically significant dose response relationship in the mortality of female mice with p-value = 0.0458. The pairwise comparison showed a statistically significant decreased mortality in medium, medium-high and high dose group when compared to the vehicle control group in female mice with p-value = 0.0187, p-value = 0.0002, and p-value = 0.0036, respectively.

For tumor data, following the multiple testing adjustment method described above, this reviewer's analyses showed no tumor types with a statistically significant positive dose response relationship in tumor incidences with increased BAY 1021189 dose in either sex of mice. The pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidences in BAY 1021189 treated groups, when compare to the vehicle control group in either male or female mice.

Malick Mbodj, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D. Team Leader, DBVI
Hepei Chen, secondary reviewer

cc:
Archival NDA (b) (4) BAY 1021189
Dr. Tsong Dr. Rahman
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5. Appendix

Table1A: Intercurrent Mortality Rate
Male Rats

	0mg|kg|day Vehicle Control		0mg|kg|day Water Control		2mg|kg|day		6mg|kg|day		20mg|kg|day	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	1	1.67	1	1.67	.	.	.	.	5	8.33
53 - 78	5	10.00	4	8.33	4	6.67	2	3.33	1	10.00
79 - 92	6	20.00	1	10.00	9	21.67	9	18.33	6	20.00
93 - 104	13	41.67	17	38.33	10	38.33	13	40.00	10	36.67
Ter. Sac.	35	58.33	37	61.67	37	61.67	36	60.00	38	63.33
Total	60	100.00	60	100.00	60	100.00	60	100.00	60	100.00

Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded

Table1B: Intercurrent Mortality Rate
Female Rats

	0mg|kg|day Vehicle Control		0mg|kg|day Water Control		2mg|kg|day		6mg|kg|day		20mg|kg|day	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	.	.	.	.	1	1.67	.	.	5	8.33
53 - 78	2	3.33	4	6.67	4	8.33	6	10.00	3	13.33
79 - 92	9	18.33	6	16.67	9	23.33	5	18.33	2	16.67
93 - 104	10	35.00	14	40.00	6	33.33	12	38.33	15	41.67
Ter. Sac.	39	65.00	36	60.00	40	66.67	37	61.67	35	58.33
Total	60	100.00	60	100.00	60	100.00	60	100.00	60	100.00

Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded

Table 2A: Intercurrent Mortality Comparison for
Male Rats

Test Statistics	P-value for Vehicle Cont. Low, Med, high	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs High
Dose-Response (Likelihood Ratio)	0.7146	0.8033	0.8542	0.6889
Homogeneity (Log-Rank)	0.9802	0.8013	0.8528	0.6864

Table 2B: Intercurrent Mortality Comparison for
Female Rats

Test Statistics	P-value for Vehicle Cont. Low, Med, high	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs High
Dose-Response (Likelihood Ratio)	0.4338	0.9362	0.6829	0.5192
Homogeneity (Log-Rank)	0.8573	0.9358	0.6810	0.5155

Table3A: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Male Rate Poly-3 Test

Organ Name	Tumor Name	0 mg Vehicle Cont (N=60) P - Trend	0 mg Water Cont(N=60) P - VC vs. W	2 mg Low (N=60) P - VC vs. L	6 mg Med (N=60) P- VC vs. M	20 mg High (N=60) P - VC vs. H
Adrenal	B-Adenoma, Cortical	2/60 (51) 0.8918	0/60 (53) NC	0/60 (51) 1.0000	1/60 (52) 0.8822	0/60 (50) 1.0000
	B-Phaeochromocytoma, Benign	4/60 (51) 0.0183	2/60 (53) NC	4/60 (52) 0.6532	6/60 (53) 0.3955	10/60 (50) 0.0686
	M-Osteosarcoma	0/60 (51) 0.2451	0/60 (53) NC	0/60 (51) NC	0/60 (52) NC	1/60 (50) 0.4950
	M-Phaeochromocytoma, Malignant	0/60 (51) 0.5024	1/60 (53) NC	0/60 (51) NC	1/60 (53) 0.5096	0/60 (50) NC
	B-Phaeochromocytoma, Benign/ M-Phaeochromocytoma, Malignant	4/60 (51) 0.0210	3/60 (53) NC	4/60 (52) 0.6532	7/60 (53) 0.2856	10/60 (50) 0.0686
Bone, Other	B-Chondroma	0/60 (51) 0.7500	0/60 (53) NC	1/60 (51) 0.5000	0/60 (52) NC	0/60 (50) NC
Brain	B-Tumour, Granular Cell, Benign	3/60 (51) 0.6794	3/60 (54) NC	3/60 (52) 0.6702	2/60 (52) 0.8247	2/60 (50) 0.8126
	M-Astrocytoma, Malignant	0/60 (51) 0.5000	1/60 (54) NC	0/60 (51) NC	1/60 (52) 0.5049	0/60 (50) NC
	M-Glioma, Mixed, Malignant	0/60 (51) 0.5024	0/60 (53) NC	0/60 (51) NC	1/60 (53) 0.5096	0/60 (50) NC
	M-Meningioma, Malignant	1/60 (52) 1.0000	0/60 (53) NC	0/60 (51) 1.0000	0/60 (52) 1.0000	0/60 (50) 1.0000
	M-Tumour, Granular Cell, Malignant	0/60 (51) NC	3/60 (53) NC	0/60 (51) NC	0/60 (52) NC	0/60 (50) NC
Connective Tissue	M-Mesothelioma	1/60 (51) 1.0000	0/60 (53) NC	0/60 (51) 1.0000	0/60 (52) 1.0000	0/60 (50) 1.0000
Duodenum	B-Leiomyoma	0/60 (51) NC	1/60 (53) NC	0/60 (51) NC	0/60 (52) NC	0/60 (50) NC
Epididymis	B-Osteoma	0/60 (51) 0.7500	0/60 (53) NC	1/60 (51) 0.5000	0/60 (52) NC	0/60 (50) NC
	M-Mesothelioma, Malignant	0/60 (51) 0.5000	0/60 (53) NC	0/60 (51) NC	1/60 (52) 0.5049	0/60 (50) NC
Eye	M-Melanoma, Malignant	0/59 (50) 0.5049	0/60 (53) NC	0/60 (51) NC	1/60 (53) 0.5146	0/60 (50) NC
Femur + Marrow	B-Osteoma	0/60 (51) 0.5000	0/60 (53) NC	0/60 (51) NC	1/60 (52) 0.5049	0/60 (50) NC
Haemolympho-Reticular System	M-Granulocytic Leukaemia	1/60 (52) 0.4348	0/60 (53) NC	0/60 (51) 1.0000	0/60 (52) 1.0000	1/60 (51) 0.7476
	M-Lymphocytic Leukaemia	1/60 (52) 0.7488	2/60 (54) NC	0/60 (51) 1.0000	1/60 (52) 0.7524	0/60 (50) 1.0000
	M-Malignant Lymphoma-Lymphoblastic	1/60 (51) 1.0000	1/60 (54) NC	0/60 (51) 1.0000	0/60 (52) 1.0000	0/60 (50) 1.0000
	M-Malignant Lymphoma-Lymphocytic	0/60 (51) 0.5000	0/60 (53) NC	0/60 (51) NC	1/60 (52) 0.5049	0/60 (50) NC
Harderian Gland	M-Adenocarcinoma	1/60 (51) 1.0000	0/60 (53) NC	0/60 (51) 1.0000	0/60 (52) 1.0000	0/60 (50) 1.0000
Heart	B-Paraganglioma	1/60 (51) 1.0000	0/60 (53) NC	0/60 (51) 1.0000	0/60 (52) 1.0000	0/60 (50) 1.0000

Male Rate Poly-3 Test

Organ Name	Tumor Name	0 mg Vehicle Cont (N=60) P - Trend	0 mg Water Cont(N=60) P - VC vs. W	2 mg Low (N=60) P - VC vs. L	6 mg Med (N=60) P- VC vs. M	20 mg High (N=60) P - VC vs. H
	M-Schwannoma, Endocardial, Malignant	1/60 (51) 0.4366	0/60 (53) NC	0/60 (51) 1.0000	0/60 (52) 1.0000	1/60 (51) 0.7525
Jejunum	B-Adenoma	0/60 (51) 0.7500	0/59 (52) NC	1/60 (51) 0.5000	0/60 (52) NC	0/59 (50) NC
Kidney	M-Liposarcoma	0/60 (51) 0.5000	0/60 (53) NC	0/60 (51) NC	1/60 (52) 0.5049	0/60 (50) NC
Liver	B-Adenoma, Hepatocellular	0/60 (51) 0.2451	1/60 (53) NC	0/60 (51) NC	0/60 (52) NC	1/60 (50) 0.4950
	M-Carcinoma, Hepatocellular	0/60 (51) 0.1878	0/60 (53) NC	0/60 (51) NC	1/60 (52) 0.5049	1/60 (51) 0.5000
	B-Adenoma, Hepatocellular/ M-Carcinoma, Hepatocellular	0/60 (51) 0.0616	1/60 (53) NC	0/60 (51) NC	1/60 (52) 0.5049	2/60 (51) 0.2475
Lung	B-Adenoma, Bronchiolo-Alveolar	0/60 (51) 0.5000	0/60 (53) NC	0/60 (51) NC	1/60 (52) 0.5049	0/60 (50) NC
Lymph Node, Mandibular	B-Haemangioma	1/60 (51) 1.0000	0/59 (52) NC	0/59 (50) 1.0000	0/60 (52) 1.0000	0/60 (50) 1.0000
Lymph Node, Mesenteric	B-Haemangioma	3/60 (51) 0.9948	2/59 (52) NC	3/60 (51) 0.6610	0/59 (51) 1.0000	0/58 (49) 1.0000
Mandibular Salivary Gland	M-Adenocarcinoma	0/60 (51) NC	1/60 (53) NC	0/60 (51) NC	0/60 (52) NC	0/60 (50) NC
Muscle, Other	M-Sarcoma Nos	0/60 (51) 0.2488	0/60 (53) NC	0/60 (51) NC	0/60 (52) NC	1/60 (51) 0.5000
Pancreas	B-Adenoma, Acinar Cell	1/60 (51) 1.0000	0/60 (53) NC	0/60 (51) 1.0000	0/60 (52) 1.0000	0/60 (50) 1.0000
	B-Adenoma, Islet Cell	4/60 (51) 0.6296	3/60 (53) NC	4/60 (52) 0.6532	0/60 (52) 1.0000	3/60 (51) 0.7818
	M-Carcinoma, Islet Cell	1/60 (51) 0.7537	0/60 (53) NC	0/60 (51) 1.0000	1/60 (53) 0.7619	0/60 (50) 1.0000
	B-Adenoma, Islet Cell/ M-Carcinoma, Islet Cell	5/60 (51) 0.7288	3/60 (53) NC	4/60 (52) 0.7658	1/60 (53) 0.9881	3/60 (51) 0.8655
Parathyroid	B-Adenoma	0/55 (46) 0.4863	0/55 (48) NC	0/56 (48) NC	1/51 (45) 0.4945	0/53 (44) NC
Pituitary	B-Adenoma, Pars Distalis	25/60 (55) 0.8949	23/60 (55) NC	25/59 (57) 0.6405	25/60 (57) 0.6405	18/59 (52) 0.9101
	B-Adenoma, Pars Intermedia	0/60 (51) 0.4320	1/60 (53) NC	2/59 (51) 0.2475	2/60 (52) 0.2524	1/59 (50) 0.4950
	B-Adenoma, Pars Distalis/ B-Adenoma, Pars Intermedia	25/60 (55) 0.8969	24/60 (55) NC	27/60 (58) 0.5287	27/60 (57) 0.4946	19/60 (53) 0.8872
Preputial/ Clitoral Gland	B-Papilloma, Squamous Cell	0/60 (51) 0.7488	0/60 (53) NC	1/60 (51) 0.5000	0/60 (52) NC	0/59 (49) NC
	M-Carcinoma, Squamous Cell	0/60 (51) 0.1847	2/60 (54) NC	0/60 (51) NC	1/60 (52) 0.5049	1/59 (50) 0.4950
Skin/Subcutis	B-Dermal Fibroma	0/60 (51) 0.0597	1/60 (53) NC	0/60 (51) NC	1/59 (52) 0.5049	2/60 (50) 0.2426
	B-Fibroma	2/60 (51) 0.8862	1/60 (54) NC	1/60 (51) 0.8787	2/59 (52) 0.6985	0/60 (50) 1.0000
	B-Keratoacanthoma	3/60 (52) 0.6704	1/60 (53) NC	3/60 (52) 0.6609	1/59 (52) 0.9411	2/60 (50) 0.8063

Male Rate Poly-3 Test

Organ Name	Tumor Name	0 mg Vehicle Cont (N=60) P - Trend	0 mg Water Cont(N=60) P - VC vs. W	2 mg Low (N=60) P - VC vs. L	6 mg Med (N=60) P- VC vs. M	20 mg High (N=60) P - VC vs. H
	B-Lipoma	1/60 (51) 0.1667	1/60 (53) NC	0/60 (51) 1.0000	1/59 (52) 0.7573	2/60 (51) 0.5000
	B-Papilloma, Squamous Cell	1/60 (52) 0.4292	0/60 (53) NC	0/60 (51) 1.0000	0/59 (52) 1.0000	1/60 (50) 0.7426
	B-Tumour, Hair Follicle, Beign	2/60 (51) 0.8349	1/60 (53) NC	4/60 (52) 0.3483	3/59 (52) 0.5093	1/60 (50) 0.8750
	M-Basal Cell Tumour, Malignant	0/60 (51) 0.2451	0/60 (53) NC	0/60 (51) NC	0/59 (52) NC	1/60 (50) 0.4950
	M-Carcinoma, Squamous Cell	0/60 (51) NC	2/60 (54) NC	0/60 (51) NC	0/59 (52) NC	0/60 (50) NC
	M-Fibrosarcoma	1/60 (52) 0.5276	1/60 (54) NC	1/60 (52) 0.7524	0/59 (52) 1.0000	1/60 (51) 0.7476
	M-Schwannoma, Malignant	0/60 (51) 0.5000	0/60 (53) NC	0/60 (51) NC	1/59 (52) 0.5049	0/60 (50) NC
Stomach	B-Papilloma, Squamous Cell	0/60 (51) 0.2488	0/60 (53) NC	0/60 (51) NC	0/60 (52) NC	1/60 (51) 0.5000
Sublingual Salivary Gland	B-Adenoma	0/60 (51) 0.2451	0/60 (53) NC	0/60 (51) NC	0/60 (52) NC	1/60 (50) 0.4950
Testis	B-Adenoma, Leydig Cell	2/60 (51) 0.0076	0/60 (53) NC	1/60 (52) 0.8822	0/60 (52) 1.0000	6/60 (50) 0.1281
	M-Mesothelioma, Malignant	0/60 (51) 0.5000	0/60 (53) NC	0/60 (51) NC	1/60 (52) 0.5049	0/60 (50) NC
Thymus	B-Thymoma, Benign	3/54 (46) 0.4027	4/58 (51) NC	4/58 (50) 0.5470	2/56 (49) 0.8383	4/59 (50) 0.5470
	M-Thymoma, Malignant	0/54 (46) 0.7641	0/58 (51) NC	1/58 (50) 0.5208	0/56 (49) NC	0/59 (50) NC
	B-Thymoma, Benign/ M-Thymoma, Malignant	3/60 (51) 0.4274	4/60 (53) NC	5/60 (52) 0.3687	2/60 (52) 0.8247	4/60 (50) 0.4888
Thyroid	B-Adenoma, C-Cell	5/60 (51) 0.3756	11/60 (55) NC	6/60 (53) 0.5274	6/60 (53) 0.5274	6/59 (49) 0.4715
	B-Adenoma, Follicular Cell	3/60 (51) 0.5372	6/60 (53) NC	4/60 (51) 0.5000	2/60 (52) 0.8247	3/59 (49) 0.6418
	M-Carcinoma, C-Cell	0/60 (51) 0.2414	0/60 (53) NC	0/60 (51) NC	0/60 (52) NC	1/59 (49) 0.4900
	M-Carcinoma, Follicular Cell	0/60 (51) 0.5000	0/60 (53) NC	0/60 (51) NC	1/60 (53) 0.5096	0/59 (49) NC
	B-Adenoma, C-Cell/ M-Carcinoma, C-Cell	5/60 (51) 0.2655	11/60 (55) NC	6/60 (53) 0.5274	6/60 (53) 0.5274	7/60 (50) 0.3658
	B-Adenoma, Follicular Cell/ M-Carcinoma, Follicular Cell	3/60 (51) 0.5577	6/60 (53) NC	4/60 (51) 0.5000	3/60 (53) 0.6791	3/60 (50) 0.6516
Zymbal Gland	B-Adenoma, Sebaceous Cell	0/59 (50) 0.2423	0/58 (51) NC	0/56 (47) NC	0/57 (50) NC	1/56 (47) 0.4845
	B-Papilloma, Squamous Cell	0/59 (50) 0.4974	0/58 (51) NC	0/56 (47) NC	1/57 (50) 0.5000	0/56 (46) NC
	M-Carcinoma	0/59 (50) 0.1833	0/58 (51) NC	0/56 (47) NC	1/57 (50) 0.5000	1/56 (47) 0.4845

Table3B: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Female Rats Poly-3 Test

Organ Name	Tumor Name	0 mg Vehicle Cont (N=60) P - Trend	0 mg Water Cont (N=60) P - VC vs. W	2 mg Low (N=60) P - VC vs. L	6 mg Med (N=60) P- VC vs. M	20 mg High (N=60) P - VC vs. H
Adrenal	B-Adenoma, Cortical	1/60 (53) 0.3776	0/60 (52) NC	0/60 (52) 1.0000	1/60 (51) 0.7427	1/60 (50) 0.7377
	B-Phaeochromocytoma, Benign	0/60 (53) 0.6147	2/60 (52) NC	1/60 (52) 0.4952	1/60 (52) 0.4952	0/60 (50) NC
	M-Carcinoma, Cortical	0/60 (53) 0.7427	0/60 (52) NC	1/60 (52) 0.4952	0/60 (51) NC	0/60 (50) NC
	B-Adenoma, Cortical/ M-Carcinoma, Cortical	1/60 (53) 0.4974	0/60 (52) NC	1/60 (52) 0.7476	1/60 (51) 0.7427	1/60 (50) 0.7377
Bone, Other	M-Osteosarcoma	0/60 (53) 0.2427	0/60 (52) NC	0/60 (52) NC	0/60 (51) NC	1/60 (50) 0.4854
Brain	B-Tumour, Granular Cell, Benign	3/60 (53) 1.0000	2/60 (52) NC	0/60 (52) 1.0000	0/60 (51) 1.0000	0/60 (50) 1.0000
	M-Medulloblastoma	0/60 (53) 0.4928	0/60 (52) NC	0/60 (52) NC	1/60 (52) 0.4952	0/60 (50) NC
	M-Tumour, Granular Cell, Malignant	1/60 (53) 1.0000	0/60 (52) NC	0/60 (52) 1.0000	0/60 (51) 1.0000	0/60 (50) 1.0000
	B-Tumour, Granular Cell, Benign / M-Tumour, Granular Cell, Malignant	4/60 (53) 1.0000	2/60 (52) NC	0/60 (52) 1.0000	0/60 (51) 1.0000	0/60 (50) 1.0000
Connective Tissue	B-Lipoma	0/60 (53) 0.2427	0/60 (52) NC	0/60 (52) NC	0/60 (51) NC	1/60 (50) 0.4854
Haemolympho-Reticular System	M-Histiocytic Sarcoma	0/60 (53) 0.2427	0/60 (52) NC	0/60 (52) NC	0/60 (51) NC	1/60 (50) 0.4854
	M-Lymphocytic Leukaemia	1/60 (53) 0.5244	1/60 (52) NC	1/60 (53) 0.7524	0/60 (51) 1.0000	1/60 (51) 0.7427
Heart	B-Paraganglioma	0/60 (53) 0.4903	0/60 (52) NC	0/60 (52) NC	1/60 (51) 0.4904	0/60 (50) NC
Liver	B-Adenoma, Hepatocellular	1/60 (53) 0.3545	0/60 (52) NC	0/60 (52) 1.0000	2/60 (51) 0.4854	1/60 (50) 0.7377
	B-Cholangioma	0/60 (53) 0.4903	0/60 (52) NC	0/60 (52) NC	1/60 (51) 0.4904	0/60 (50) NC
Mammary Gland	B-Adenoma	2/56 (49) 0.8894	1/60 (52) NC	0/59 (51) 1.0000	1/58 (50) 0.8825	0/56 (48) 1.0000
	B-Fibroadenoma	7/56 (50) 0.6893	11/60 (54) NC	9/59 (52) 0.4266	9/58 (51) 0.4099	6/56 (48) 0.6962
	M-Adenocarcinoma	3/56 (50) 0.9412	2/60 (52) NC	1/59 (51) 0.9436	2/58 (51) 0.8250	0/56 (48) 1.0000

Female Rats Poly-3 Test

Organ Name	Tumor Name	0 mg Vehicle Cont (N=60) P - Trend	0 mg Water Cont (N=60) P - VC vs. W	2 mg Low (N=60) P - VC vs. L	6 mg Med (N=60) P- VC vs. M	20 mg High (N=60) P - VC vs. H
	M-Adenocarcinoma Arising in Fibroadenoma	0/56 (49) NC	1/60 (52) NC	0/59 (51) NC	0/58 (50) NC	0/56 (48) NC
Muscle, Biceps Femoris	B-Hemangioma	0/60 (53) 0.2464	0/59 (51) NC	0/60 (52) NC	0/60 (51) NC	1/60 (51) 0.4904
Nasal Cavity	B-Chondroma	0/60 (53) 0.4903	0/60 (52) NC	0/60 (52) NC	1/60 (51) 0.4904	0/60 (50) NC
Ovary	B-Adenoma, Tubulostromal	0/60 (53) 0.6284	0/60 (52) NC	1/60 (52) 0.4952	2/60 (51) 0.2381	0/60 (50) NC
	B-Benign Thecoma	1/60 (53) 1.0000	0/60 (52) NC	0/60 (52) 1.0000	0/60 (51) 1.0000	0/60 (50) 1.0000
	B-Cystadenoma	0/60 (53) 0.7427	0/60 (52) NC	1/60 (52) 0.4952	0/60 (51) NC	0/60 (50) NC
	B-Luteoma, Benign	0/60 (53) NC	1/60 (52) NC	0/60 (52) NC	0/60 (51) NC	0/60 (50) NC
	B-Tumour, Granulosa Cell, Benign	2/60 (53) 0.1517	0/60 (52) NC	4/60 (52) 0.3300	3/60 (51) 0.4816	5/60 (50) 0.1949
	B-Tumour, Sex Cord Stromal, mixed, benign	1/60 (53) 0.1578	2/60 (52) NC	0/60 (52) 1.0000	2/60 (52) 0.4928	2/60 (50) 0.4779
Pancreas	B-Adenoma, Islet Cell	0/60 (53) 0.4903	0/60 (52) NC	0/60 (52) NC	1/60 (51) 0.4904	0/60 (50) NC
	M-Adenocarcinoma, Ductal Cell	0/60 (53) 0.4903	0/60 (52) NC	0/60 (52) NC	1/60 (51) 0.4904	0/60 (50) NC
Parathyroid	B-Adenoma	0/52 (45) NC	2/52 (44) NC	0/53 (46) NC	0/52 (44) NC	0/56 (47) NC
Pituitary	B-Adenoma, Pars Distalis	25/60 (57) 0.3768	37/59 (58) NC	26/60 (55) 0.4314	27/60 (56) 0.3915	26/60 (54) 0.3964
	B-Adenoma, Pars Intermedia	3/60 (53) 0.8279	0/59 (51) NC	2/60 (52) 0.8126	0/60 (51) 1.0000	1/60 (50) 0.9338
	M-Carcinoma, Pars Distalis	2/60 (53) 0.8754	2/59 (51) NC	5/60 (53) 0.2185	2/60 (52) 0.6839	1/60 (51) 0.8714
	B-Adenoma/ M-Carcinoma, Pars Distalis/ B-Adenoma, Pars Intermedia	30/60 (58) 0.6568	39/60 (59) NC	33/60 (57) 0.3167	29/60 (57) 0.6092	28/60 (55) 0.6082
Preputial/ Clitoral Gland	M-Carcinoma, Squamous Cell	0/60 (53) 0.1788	0/59 (51) NC	0/60 (52) NC	1/60 (51) 0.4904	1/60 (50) 0.4854
Skin/Subcutis	B-Dermal Fibroma	0/60 (53) 0.7427	0/60 (52) NC	1/60 (52) 0.4952	0/60 (51) NC	0/60 (50) NC
	B-Fibroma	1/60 (53) 1.0000	1/60 (52) NC	0/60 (52) 1.0000	0/60 (51) 1.0000	0/60 (50) 1.0000

Female Rats Poly-3 Test

Organ Name	Tumor Name	0 mg Vehicle Cont (N=60) P - Trend	0 mg Water Cont (N=60) P - VC vs. W	2 mg Low (N=60) P - VC vs. L	6 mg Med (N=60) P- VC vs. M	20 mg High (N=60) P - VC vs. H
	B-Lipoma	0/60 (53) NC	1/60 (52) NC	0/60 (52) NC	0/60 (51) NC	0/60 (50) NC
	B-Tumour, Hair Follicle, Benign	0/60 (53) 0.7427	0/60 (52) NC	1/60 (52) 0.4952	0/60 (51) NC	0/60 (50) NC
	M-Basal Cell Tumour, Malignant	1/60 (53) 1.0000	0/60 (52) NC	0/60 (52) 1.0000	0/60 (51) 1.0000	0/60 (50) 1.0000
	M-Fibrosarcoma	2/60 (53) 0.5678	1/60 (53) NC	0/60 (52) 1.0000	0/60 (51) 1.0000	1/60 (50) 0.8675
	M-Sarcoma Nos	0/60 (53) 0.2427	0/60 (52) NC	0/60 (52) NC	0/60 (51) NC	1/60 (50) 0.4854
Thoracic Cavity	M-Schwannoma, Malignant	0/60 (53) 0.2427	0/60 (52) NC	0/60 (52) NC	0/60 (51) NC	1/60 (50) 0.4854
Thymus	B-Thymoma, Benign	8/56 (50) 0.9292	10/57 (50) NC	6/56 (48) 0.7827	10/58 (50) 0.3976	3/57 (47) 0.9675
	M-Thymoma, Malignant	1/56 (49) 0.8262	1/57 (49) NC	1/56 (48) 0.7474	1/58 (49) 0.7526	0/57 (47) 1.0000
	B-Thymoma, Benign/ M-Thymoma, Malignant	9/60 (54) 0.9558	11/60 (53) NC	7/60 (52) 0.7673	11/60 (52) 0.3662	3/60 (50) 0.9801
Thyroid	B-Adenoma, C-Cell	6/60 (53) 0.3886	9/60 (53) NC	5/60 (53) 0.7370	5/60 (51) 0.7144	6/60 (50) 0.5778
	B-Adenoma, Follicular Cell	2/60 (53) 0.8272	1/60 (52) NC	4/60 (52) 0.3300	3/60 (51) 0.4816	1/60 (50) 0.8675
	M-Carcinoma, C-Cell	0/60 (53) 0.2427	0/60 (52) NC	0/60 (52) NC	0/60 (51) NC	1/60 (50) 0.4854
	M-Carcinoma, Follicular Cell	0/60 (53) NC	1/60 (52) NC	0/60 (52) NC	0/60 (51) NC	0/60 (50) NC
	B-Adenoma, C-Cell/ M-Carcinoma, C-Cell	6/60 (53) 0.2749	9/60 (53) NC	5/60 (53) 0.7370	5/60 (51) 0.7144	7/60 (51) 0.4700
	B-Adenoma, Follicular Cell/ M-Carcinoma, Follicular Cell	2/60 (53) 0.8272	2/60 (52) NC	4/60 (52) 0.3300	3/60 (51) 0.4816	1/60 (50) 0.8675
Uterus	B-Adenoma	0/60 (53) 0.2427	0/60 (52) NC	0/60 (52) NC	0/60 (51) NC	1/60 (50) 0.4854
	B-Benign Granular Cell Tumour	0/60 (53) 0.7427	0/60 (52) NC	1/60 (52) 0.4952	0/60 (51) NC	0/60 (50) NC
	B-Polyp, Endometrial Stromal	10/60 (53) 0.0772	5/60 (52) NC	10/60 (52) 0.5793	9/60 (52) 0.6771	15/60 (52) 0.1658
	M-Adenocarcinoma	3/60 (53) 0.3057	0/60 (52) NC	1/60 (52) 0.9387	2/60 (51) 0.8064	3/60 (50) 0.6327

Female Rats Poly-3 Test

Organ Name	Tumor Name	0 mg Vehicle Cont (N=60) P - Trend	0 mg Water Cont (N=60) P - VC vs. W	2 mg Low (N=60) P - VC vs. L	6 mg Med (N=60) P- VC vs. M	20 mg High (N=60) P - VC vs. H
	M-Carcinoma	0/60 (53) 0.3019	0/60 (52) NC	1/60 (52) 0.4952	0/60 (51) NC	1/60 (50) 0.4854
	M-Carcinoma, Squamous Cell	0/60 (53) NC	1/60 (52) NC	0/60 (52) NC	0/60 (51) NC	0/60 (50) NC
	M-Sarcoma, Endometrial Stromal	0/60 (53) 0.1908	0/60 (52) NC	0/60 (52) NC	2/60 (53) 0.2476	1/60 (50) 0.4854
	M-Schwannoma, Malignant	1/60 (53) 0.8898	1/60 (52) NC	3/60 (53) 0.3089	2/60 (52) 0.4928	0/60 (50) 1.0000
	B-Polyp, Endometrial Stromal / M-Sarcoma Endometrial Stromal	10/60 (53) 0.0519	5/60 (52) NC	10/60 (52) 0.5793	11/60 (53) 0.5000	16/60 (52) 0.1176
Vagina	M-Sarcoma, Stromal	0/60 (53) 0.7427	0/60 (52) NC	1/60 (52) 0.4952	0/60 (51) NC	0/60 (50) NC
	M-Schwannoma, Malignant	0/60 (53) 0.4928	0/60 (52) NC	0/60 (52) NC	1/60 (52) 0.4952	0/60 (50) NC
Zymbal Gland	B-Adenoma, Sebaceous Cell	0/54 (47) 0.7577	0/59 (51) NC	1/58 (51) 0.5204	0/57 (48) NC	0/57 (48) NC
	M-Carcinoma	0/54 (47) 0.1865	0/59 (51) NC	0/58 (51) NC	1/57 (48) 0.5053	1/57 (49) 0.5104

Figure 1A: Kaplan-Meier Survival Curves for
Male Rats

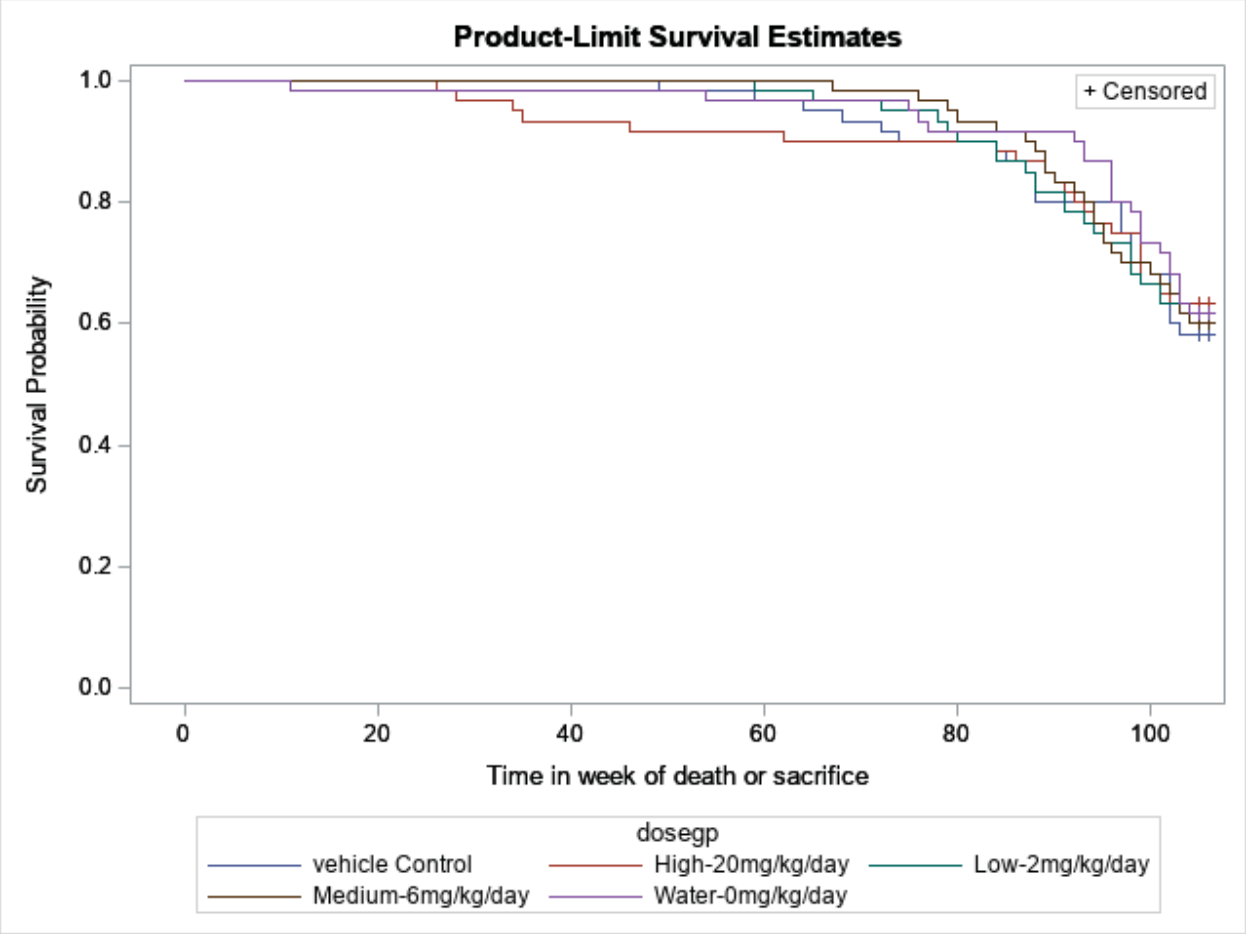


Figure 1B: Kaplan-Meier Survival Curves **for Female Rats**

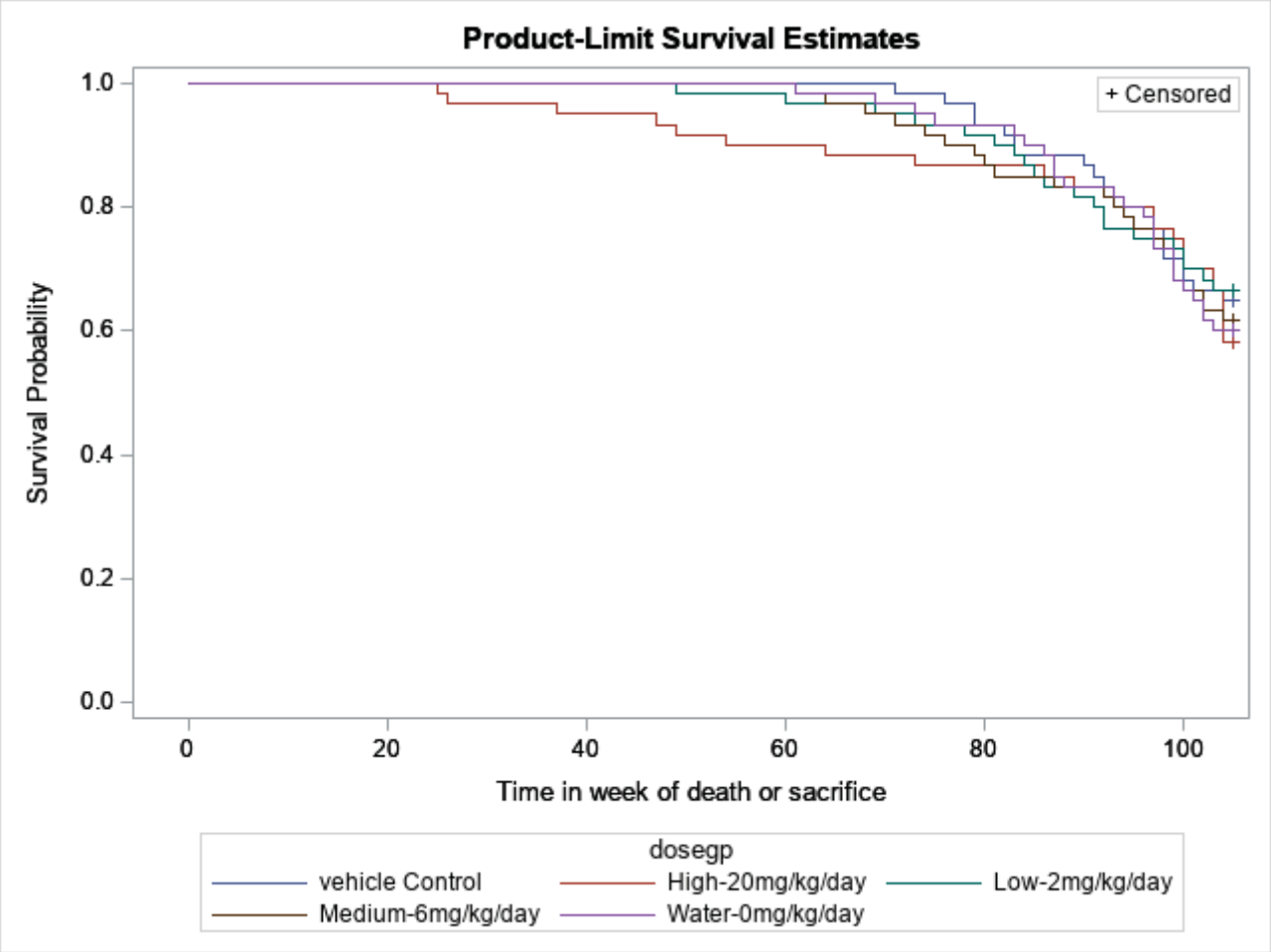


Table4A: Intercurrent Mortality Rate
Male Mice

	0mg|kg|day		5mg|kg|day		15mg|kg|day		50mg|kg|day		150mg|kg|day	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	1	1.67	1	1.67	5	8.33	2	3.33	5	8.33
53 - 78	4	8.33	8	15.00	7	20.00	8	16.67	9	23.33
79 - 92	13	30.00	10	31.67	9	35.00	10	33.33	10	40.00
93 - 104	7	41.67	6	41.67	15	60.00	13	55.00	8	53.33
Ter. Sac.	35	58.33	35	58.33	24	40.00	27	45.00	28	46.67
Total	60	100.00	60	100.00	60	100.00	60	100.00	60	100.00

Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded

Table4B: Intercurrent Mortality Rate
Female Mice

	0mg|kg|day		6mg|kg|day		20mg|kg|day		60mg|kg|day		250mg|kg|day	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	4	6.67	3	5.00	.	.	4	6.67	4	6.67
53 - 78	16	33.33	11	23.33	16	26.67	10	23.33	8	20.00
79 - 93	25	75.00	23	61.67	15	51.67	8	36.67	17	48.33
ADD	.	.	.	.	.	.	1	1.67	.	.
Ter. Sac.	15	25.00	23	38.33	29	48.33	37	61.67	31	51.67
Total	60	100.00	60	100.00	60	100.00	60	100.00	60	100.00

Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded
ADD: accidental death

Table 5A: Intercurrent Mortality Comparison for
Male Mice

Test Statistics	P-value for Veh. Cont., Low, Med, Med-high, high	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs Med-High	P-value for Vehicle Cont. vs High.
Dose-Response (Likelihood Ratio)	0.2055	0.8861	0.0577	0.1296	0.1226
Homogeneity (Log-Rank)	0.1997	0.8854	0.0556	0.1264	0.1197

Table 5B: Intercurrent Mortality Comparison for
Female Mice

Test Statistics	P-value for Veh. Cont. Low, Med, Med-high, high	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs Med-High	P-value for Vehicle Cont. vs High.
Dose-Response (Likelihood Ratio)	0.0458*	0.1219	0.0187*	0.0002*	0.0036*
Homogeneity (Log-Rank)	0.0016*	0.1135	0.0166*	0.0002*	0.0029*

* = statistically significant at the 0.05 significance level.

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and the pairwise Comparisons

Male Mice Poly-3 Test

Organ Name	Tumor Name	0 mg Cont (N=60) P - Trend	5 mg Low (N=60) P - VC vs. L	15 mg Med (N=60) P - VC vs. M	50 mg Med-High (N=60) P - VC vs. MH	150 mg High (N=60) P - VC vs. H
Abdominal Cavity	M-Sarcoma Nos	0/57 (47) 0.7892	1/57 (46) 0.4946	0/60 (44) NC	0/59 (44) NC	0/59 (42) NC
Adrenal	B-Benign Phaeochromocytoma	0/59 (49) 0.4816	0/60 (48) NC	1/59 (45) 0.4787	2/56 (42) 0.2103	0/58 (41) NC
	B-Cortical Adenoma	5/59 (51) 0.3957	1/60 (48) 0.9839	2/59 (44) 0.9178	0/56 (42) 1.0000	3/58 (41) 0.7835
	B-Subcapsular Cell Adenoma	6/59 (50) 0.7284	9/60 (49) 0.2737	9/59 (46) 0.2302	6/56 (44) 0.5267	5/58 (41) 0.6122
	M-Subcapsular Cell Carcinoma	0/59 (49) 0.5670	0/60 (48) NC	1/59 (44) 0.4731	0/56 (42) NC	0/58 (41) NC
	B-Subcapsular Cell Adenoma / M-Subcapsular Cell Carcinoma	6/59 (50) 0.7546	9/60 (49) 0.2737	10/59 (46) 0.1575	6/56 (44) 0.5267	5/58 (41) 0.6122
Caecum	B-Adenoma	0/59 (49) 0.1839	0/58 (47) NC	0/55 (42) NC	0/59 (44) NC	1/55 (41) 0.4556
Epididymis	B-Leydig Cell Adenoma	0/60 (49) 0.5764	0/60 (48) NC	1/60 (44) 0.4731	0/60 (45) NC	0/60 (43) NC
Haemolympho-Reticular System	M-Histiocytic Sarcoma	2/60 (50) 0.2599	0/60 (48) 1.0000	2/60 (45) 0.6506	1/60 (45) 0.8584	2/60 (43) 0.6325
	M-Lymphocytic Leukaemia	0/60 (49) 0.5783	0/60 (48) NC	1/60 (45) 0.4787	0/60 (45) NC	0/60 (43) NC
	M-Malignant Lymphoma-Pleomorphic	2/60 (49) 0.3276	2/60 (48) 0.6836	0/60 (44) 1.0000	1/60 (45) 0.8626	2/60 (43) 0.6406
	M-Malignant Lymphoma-Lymphocytic	2/60 (50) 0.7225	2/60 (49) 0.6837	4/60 (45) 0.2897	4/60 (45) 0.2897	1/60 (43) 0.8490
	M-Malignant Lymphoma-Lymphoblastic	0/60 (49) 0.0290	0/60 (48) NC	0/60 (44) NC	1/60 (45) 0.4787	2/60 (45) 0.2265
Harderian Gland	B-Adenoma	9/60 (51) 0.8458	10/60 (49) 0.4611	9/60 (47) 0.5266	12/60 (46) 0.2233	5/60 (44) 0.8758
	M-Adenocarcinoma	0/60 (49) 0.5783	0/60 (48) NC	1/60 (45) 0.4787	0/60 (45) NC	0/60 (43) NC
	B-Adenoma/ M-Adenocarcinoma	9/60 (51) 0.8629	10/60 (49) 0.4611	10/60 (47) 0.4208	12/60 (46) 0.2233	5/60 (44) 0.8758
Kidney	B-Adenoma	1/60 (49) 0.6773	1/60 (48) 0.7474	0/60 (44) 1.0000	3/60 (45) 0.2769	0/60 (43) 1.0000
	M-Carcinoma	0/60 (49) 0.8649	2/60 (48) 0.2423	0/60 (44) NC	0/60 (45) NC	0/60 (43) NC

Male Mice Poly-3 Test

Organ Name	Tumor Name	0 mg Cont (N=60) P - Trend	5 mg Low (N=60) P - VC vs. L	15 mg Med (N=60) P - VC vs. M	50 mg Med-High (N=60) P - VC vs. MH	150 mg High (N=60) P - VC vs. H
	B-Adenoma/ M-Carcinoma	1/60 (49) 0.8159	3/60 (48) 0.3008	0/60 (44) 1.0000	3/60 (45) 0.2769	0/60 (43) 1.0000
	M-Renal Mesenchymal Tumour	0/60 (49) 0.1878	0/60 (48) NC	0/60 (44) NC	0/60 (45) NC	1/60 (43) 0.4674
Liver	B-Haemangioma	2/60 (49) 0.1663	0/60 (48) 1.0000	0/60 (44) 1.0000	0/60 (45) 1.0000	2/60 (43) 0.6406
	B-Hepatocellular Adenoma	5/60 (50) 0.5614	10/60 (48) 0.1132	10/60 (46) 0.0964	5/60 (45) 0.5607	7/60 (44) 0.2918
	M-Haemangiosarcoma	0/60 (49) 0.7395	1/60 (48) 0.4948	1/60 (45) 0.4787	0/60 (45) NC	0/60 (43) NC
	M-Hepatocellular Carcinoma	3/60 (50) 0.9373	5/60 (50) 0.3575	7/60 (47) 0.1345	4/60 (45) 0.4407	1/60 (43) 0.9211
	B-Hepatocellular Adenoma/ M-Hepatocellular Carcinoma	8/60 (50) 0.8439	15/60 (50) 0.0765	16/60 (49) 0.0442	8/60 (45) 0.5159	8/60 (44) 0.4961
Lung	B-Bronchiolo-Alveolar Adenoma	7/60 (50) 0.9852	10/60 (50) 0.2977	10/60 (46) 0.2344	1/60 (45) 0.9956	3/60 (43) 0.9254
	M-Bronchiolo-Alveolar Carcinoma	9/60 (51) 0.3090	3/60 (48) 0.9818	10/60 (45) 0.3795	5/60 (46) 0.8929	8/60 (44) 0.5776
	B-Bronchiolo-Alveolar Adenoa/ M-Bronchiolo-Alveolar Carcinoma	15/60 (51) 0.8805	13/60 (50) 0.7272	18/60 (47) 0.2370	6/60 (46) 0.9873	10/60 (44) 0.8342
Nasal Cavity	B-Adenoma	0/60 (49) 0.5764	0/60 (48) NC	1/60 (45) 0.4787	0/59 (44) NC	0/60 (43) NC
Oral Cavity	B-Squamous Cell Papilloma	1/59 (49) 1.0000	0/60 (48) 1.0000	0/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (43) 1.0000
Pancreas	B-Islet Cell Adenoma	1/60 (50) 0.8971	1/60 (48) 0.7423	1/60 (44) 0.7197	0/60 (45) 1.0000	0/60 (43) 1.0000
Pituitary	B-Adenoma	1/60 (50) 0.1036	0/59 (47) 1.0000	3/58 (44) 0.2617	4/58 (45) 0.1497	3/58 (43) 0.2536
	M-Carcinoma	0/60 (49) 0.7331	1/59 (47) 0.4896	1/58 (43) 0.4674	0/58 (43) NC	0/58 (42) NC
	B-Adenoma/ M-Carcinoma	1/60 (50) 0.1937	1/60 (48) 0.7423	4/60 (46) 0.1559	4/60 (47) 0.1622	3/60 (44) 0.2617
Prostate	B-Adenoma	0/60 (49) 0.7860	1/60 (48) 0.4948	0/60 (44) NC	0/60 (45) NC	0/60 (43) NC
	M-Adenocarcinoma	0/60 (49) 0.5764	0/60 (48) NC	1/60 (44) 0.4731	0/60 (45) NC	0/60 (43) NC
	B-Adenoma/ M-Adenocarcinoma	0/60 (49) 0.7391	1/60 (48) 0.4948	1/60 (44) 0.4731	0/60 (45) NC	0/60 (43) NC

Male Mice Poly-3 Test

Organ Name	Tumor Name	0 mg Cont (N=60) P - Trend	5 mg Low (N=60) P - VC vs. L	15 mg Med (N=60) P - VC vs. M	50 mg Med-High (N=60) P - VC vs. MH	150 mg High (N=60) P - VC vs. H
Skin/Subcutis	B-Benign Hair Follicle Tumour	0/60 (49) 0.3870	0/60 (48) NC	0/60 (44) NC	1/60 (46) 0.4842	0/60 (43) NC
	B-Keratoacanthoma	1/60 (50) 1.0000	0/60 (48) 1.0000	0/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (43) 1.0000
	M-Fibrosarcoma	0/60 (49) 0.1878	0/60 (48) NC	0/60 (44) NC	0/60 (45) NC	1/60 (43) 0.4674
	M-Haemangiosarcoma	0/60 (49) 0.1878	0/60 (48) NC	0/60 (44) NC	0/60 (45) NC	1/60 (43) 0.4674
	M-Sarcoma Nos	1/60 (50) 1.0000	0/60 (48) 1.0000	0/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (43) 1.0000
Spleen	B-Haemangioma	1/60 (49) 1.0000	0/60 (48) 1.0000	0/60 (44) 1.0000	0/60 (45) 1.0000	0/59 (42) 1.0000
	M-Haemangiosarcoma	1/60 (49) 0.2731	2/60 (48) 0.4922	1/60 (44) 0.7251	1/60 (45) 0.7310	2/59 (42) 0.4418
Stomach	B-Benign Neuroendocrine Cell	0/60 (49) 0.1842	0/60 (48) NC	0/60 (44) NC	0/60 (45) NC	1/59 (42) 0.4615
	B-Squamous Cell Papilloma	1/60 (49) 0.3351	0/60 (48) 1.0000	0/60 (44) 1.0000	0/60 (45) 1.0000	1/59 (42) 0.7128
Tail	B-Fibroma	1/60 (49) 1.0000	0/58 (46) 1.0000	0/60 (44) 1.0000	0/57 (42) 1.0000	0/59 (42) 1.0000
	B-Haemangioma	1/60 (49) 0.3419	0/58 (46) 1.0000	0/60 (44) 1.0000	0/57 (42) 1.0000	1/59 (42) 0.7128
Testis	B-Haemangioma	0/60 (49) 0.1878	0/60 (48) NC	0/60 (44) NC	0/60 (45) NC	1/60 (43) 0.4674
	B-Leydig Cell Adenoma	4/60 (49) 0.7435	3/60 (48) 0.7736	6/60 (45) 0.3165	7/60 (45) 0.2143	2/60 (43) 0.8654
	M-Leydig Cell Carcinoma	0/60 (49) 0.4547	0/60 (48) NC	1/60 (44) 0.4731	1/60 (45) 0.4787	0/60 (43) NC
	B-Leydig Cell Adenoma/ M-Leydig Cell Carcinoma	4/60 (49) 0.7615	3/60 (48) 0.7736	7/60 (45) 0.2143	8/60 (46) 0.1483	2/60 (43) 0.8654
Thoracic Cavity	M-Malignant Mesothelioma	0/60 (49) 0.5778	0/58 (46) NC	1/60 (44) 0.4731	0/60 (45) NC	0/57 (41) NC
Thymus	B-Benign Thymoma	0/53 (44) 0.1869	1/52 (42) 0.4884	0/54 (40) NC	1/48 (36) 0.4500	1/52 (36) 0.4500
Thyroid	B-Follicular Cell Adenoma	2/60 (50) 0.7666	0/60 (48) 1.0000	0/60 (44) 1.0000	1/60 (45) 0.8584	0/60 (43) 1.0000
Urinary Bladder	B-Mesenchymal Proliferative Lesion	0/60 (49) 0.7368	1/60 (48) 0.4948	1/59 (44) 0.4731	0/60 (45) NC	0/59 (42) NC

Male Mice Poly-3 Test

Organ Name	Tumor Name	0 mg Cont (N=60) P - Trend	5 mg Low (N=60) P - VC vs. L	15 mg Med (N=60) P - VC vs. M	50 mg Med- High (N=60) P - VC vs. MH	150 mg High (N=60) P - VC vs. H
	M-Carcinoma, Transitional Cell	0/60 (49) 0.3816	0/60 (48) NC	0/59 (44) NC	1/60 (45) 0.4787	0/59 (42) NC
Whole Body	Hemangioma/Hemangiosarcoma	5/60 (49) 0.0522	3/60 (48) 0.8592	2/60 (45) 0.9301	1/60 (45) 0.9828	7/60 (44) 0.3049

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and The pairwise comparisons

Female Mice Poly-3 Test

Organ Name	Tumor Name	0 mg Cont (N=60) P - Trend	6 mg Low (N=60) P - VC vs. L	20 mg Med(N=60) P - VC vs. M	60 mg Med-High (N=60) P - VC vs. MH	250 mg High (N=60) P - VC vs. H
Abdominal Cavity	M-Fibrosarcoma	0/60 (30) 0.4099	0/60 (33) NC	0/58 (32) NC	1/59 (34) 0.5312	0/56 (32) NC
Adrenal	B-Benign phaeochromocytoma	0/60 (30) 0.8193	1/60 (33) 0.5238	0/60 (34) NC	0/60 (34) NC	0/60 (35) NC
	B-Subcapsular cell adenoma	0/60 (30) 0.4417	2/60 (34) 0.2783	0/60 (34) NC	0/60 (34) NC	1/60 (35) 0.5385
Brain	B-Benign granular cell meningioma	0/60 (30) 0.8193	1/60 (33) 0.5238	0/60 (34) NC	0/59 (34) NC	0/60 (35) NC
Connective Tissue	M-Fibrosarcoma	0/60 (30) 0.4192	0/60 (33) NC	0/60 (34) NC	1/60 (35) 0.5385	0/60 (35) NC
	M-Haemangiosarcoma	0/60 (30) 0.2156	0/60 (33) NC	0/60 (34) NC	0/60 (34) NC	1/60 (36) 0.5455
	M-Sarcoma nos	1/60 (31) 1.0000	0/60 (33) 1.0000	0/60 (34) 1.0000	0/60 (34) 1.0000	0/60 (35) 1.0000
Ear	B-Squamous cell papilloma	0/59 (30) 0.2169	0/59 (32) NC	0/60 (34) NC	0/60 (34) NC	1/60 (36) 0.5455
Femur + Marrow	B-Haemangioma	0/60 (30) 0.4192	0/60 (33) NC	0/60 (34) NC	1/60 (35) 0.5385	0/60 (35) NC
Haemolympho-reticular System	M-Histiocytic sarcoma	2/60 (31) 0.7813	2/60 (34) 0.7278	3/60 (35) 0.5585	3/60 (35) 0.5585	1/60 (35) 0.9018
	M-Leukaemia nos	0/60 (30) 0.8204	1/60 (34) 0.5312	0/60 (34) NC	0/60 (34) NC	0/60 (35) NC
	M-Lymphocytic leukaemia	0/60 (30) 0.7810	1/60 (34) 0.5312	1/60 (34) 0.5312	0/60 (34) NC	0/60 (35) NC
	M-Malignant lymphoma-pleomorphic	4/60 (32) 0.2683	0/60 (33) 1.0000	1/60 (34) 0.9775	3/60 (36) 0.8320	3/60 (36) 0.8320
	M-Malignant Lymphoma-Lymphocytic	7/60 (33) 0.9257	7/60 (36) 0.6852	9/60 (37) 0.4915	6/60 (37) 0.8007	4/60 (37) 0.9366
	M-Malignant Lymphoma-Lymphoblastic	0/60 (30) 0.6701	1/60 (33) 0.5238	1/60 (34) 0.5312	1/60 (35) 0.5385	0/60 (35) NC
Harderian Gland	B-Adenoma	2/60 (31) 0.9974	3/60 (35) 0.5585	10/60 (37) 0.0261	0/60 (34) 1.0000	0/60 (35) 1.0000
Kidney	B-Adenoma	0/60 (30) 0.2108	0/60 (33) NC	0/60 (34) NC	0/60 (34) NC	1/60 (35) 0.5385
Liver	B-Haemangioma	1/59 (30) 1.0000	0/60 (33) 1.0000	0/59 (33) 1.0000	0/60 (34) 1.0000	0/60 (35) 1.0000

Female Mice Poly-3 Test

Organ Name	Tumor Name	0 mg Cont (N=60) P - Trend	6 mg Low (N=60) P - VC vs. L	20 mg Med(N=60) P - VC vs. M	60 mg Med-High (N=60) P - VC vs. MH	250 mg High (N=60) P - VC vs. H
	B-Hepatocellular adenoma	0/59 (30) 0.4217	0/60 (33) NC	0/59 (33) NC	1/60 (35) 0.5385	0/60 (35) NC
	M-Haemangiosarcoma	0/59 (30) 0.6205	0/60 (33) NC	1/59 (34) 0.5312	0/60 (34) NC	0/60 (35) NC
	M-Hepatocellular carcinoma	0/59 (30) 0.6205	0/60 (33) NC	1/59 (34) 0.5312	0/60 (34) NC	0/60 (35) NC
	B-Hepatocellular adenoma / M-Hepatocellular carcinoma	0/59 (30) 0.5050	0/60 (33) NC	1/59 (34) 0.5312	1/60 (35) 0.5385	0/60 (35) NC
Lung	B-Bronchiolo-alveolar adenoa	1/60 (30) 0.9642	3/60 (34) 0.3555	5/60 (35) 0.1376	4/60 (36) 0.2399	0/60 (35) 1.0000
	M-Bronchiolo-alveolar carcinoma	4/60 (31) 0.7639	5/60 (35) 0.5792	4/60 (35) 0.7127	3/60 (35) 0.8337	3/60 (36) 0.8434
Mammary Gland	B-Bronchiolo-alveolar adenoa/ M-Bronchiolo-alveolar carcinoma	5/60 (32) 0.9549	8/60 (36) 0.3532	9/60 (37) 0.2772	7/60 (37) 0.4856	3/60 (36) 0.9050
	M-Adenocarcinoma	2/60 (31) 0.9182	2/59 (33) 0.7170	2/58 (33) 0.7170	4/58 (34) 0.3818	0/58 (33) 1.0000
	M-Adenosquamous carcinoma	0/60 (30) 0.4125	0/59 (32) NC	0/58 (32) NC	1/58 (33) 0.5238	0/58 (33) NC
Nasal Cavity	B-Fibroma	0/60 (30) 0.8204	1/60 (34) 0.5312	0/60 (34) NC	0/60 (34) NC	0/60 (35) NC
Ovary	B-Benign granulosa cell tum*	0/60 (30) 0.0865	1/59 (33) 0.5238	0/59 (33) NC	1/60 (35) 0.5385	2/60 (35) 0.2861
	B-Benign luteoma	0/60 (30) 0.2963	1/59 (33) 0.5238	3/59 (34) 0.1436	0/60 (34) NC	2/60 (35) 0.2861
	B-Benign mixed sex cord str*	0/60 (30) 0.2121	0/59 (33) NC	0/59 (33) NC	0/60 (34) NC	1/60 (35) 0.5385
	B-Cystadenoma	0/60 (30) 0.4327	1/59 (33) 0.5238	2/59 (34) 0.2783	2/60 (35) 0.2861	1/60 (35) 0.5385
	B-Leiomyoma	0/60 (30) 0.4217	0/59 (33) NC	0/59 (33) NC	1/60 (35) 0.5385	0/60 (35) NC
	B-Tubulostromal adenoma	0/60 (30) 0.0366	0/59 (33) NC	0/59 (33) NC	1/60 (35) 0.5385	2/60 (35) 0.2861
Pancreas	B-Islet cell adenoma	0/59 (30) 0.2404	1/60 (34) 0.5312	0/58 (33) NC	1/60 (35) 0.5385	1/59 (34) 0.5312
Pituitary	B-Adenoma	3/57 (31) 0.4355	4/57 (34) 0.5529	1/58 (33) 0.9505	3/58 (35) 0.7204	3/54 (32) 0.6794
Skin/Subcutis	B-Benign basal cell tumour	0/60 (30) 0.2108	0/60 (33) NC	0/60 (34) NC	0/60 (34) NC	1/60 (35) 0.5385

Female Mice Poly-3 Test

Organ Name	Tumor Name	0 mg Cont (N=60) P - Trend	6 mg Low (N=60) P - VC vs. L	20 mg Med(N=60) P - VC vs. M	60 mg Med-High (N=60) P - VC vs. MH	250 mg High (N=60) P - VC vs. H
	B-Squamous cell papilloma	1/60 (30) 1.0000	0/60 (33) 1.0000	0/60 (34) 1.0000	0/60 (34) 1.0000	0/60 (35) 1.0000
	M-Fibrosarcoma	2/60 (31) 1.0000	0/60 (33) 1.0000	0/60 (34) 1.0000	0/60 (34) 1.0000	0/60 (35) 1.0000
	M-Fibrosarcoma, pleiomorphic	0/60 (30) 0.8204	1/60 (34) 0.5312	0/60 (34) NC	0/60 (34) NC	0/60 (35) NC
Spleen	M-Haemangiosarcoma	1/59 (30) 0.7703	0/60 (33) 1.0000	2/59 (34) 0.5476	1/60 (35) 0.7909	0/60 (35) 1.0000
Thymus	B-Benign thymoma	1/54 (28) 0.3754	0/58 (32) 1.0000	4/57 (34) 0.2437	3/56 (34) 0.3835	2/56 (33) 0.5624
Thyroid	B-Follicular cell adenoma	1/60 (30) 1.0000	0/59 (33) 1.0000	0/59 (33) 1.0000	0/60 (34) 1.0000	0/60 (35) 1.0000
Uterus	B-Haemangioma	1/60 (31) 0.7663	1/60 (34) 0.7764	0/60 (34) 1.0000	4/60 (35) 0.2179	0/60 (35) 1.0000
	B-Leiomyoma	1/60 (30) 0.8448	5/60 (35) 0.1376	2/60 (34) 0.5476	3/60 (35) 0.3673	1/60 (35) 0.7909
	B-Polyp, endometrial stromal	1/60 (30) 0.6025	8/60 (36) 0.0271	8/60 (36) 0.0271	3/60 (36) 0.3789	5/60 (37) 0.1543
	B-Polyp, glandular	0/60 (30) 0.6205	0/60 (33) NC	1/60 (34) 0.5312	0/60 (34) NC	0/60 (35) NC
	M-Haemangiosarcoma	1/60 (31) 0.1081	0/60 (33) 1.0000	0/60 (34) 1.0000	1/60 (35) 0.7832	2/60 (36) 0.5567
	M-Histiocytic sarcoma	1/60 (30) 0.1176	0/60 (33) 1.0000	0/60 (34) 1.0000	0/60 (34) 1.0000	2/60 (36) 0.5691
	M-Leiomyosarcoma	1/60 (31) 0.6612	0/60 (33) 1.0000	0/60 (34) 1.0000	1/60 (35) 0.7832	0/60 (35) 1.0000
	B-Leiomyoma / M-Leiomyosarcoma	2/60 (31) 0.8827	5/60 (35) 0.2671	2/60 (34) 0.7278	4/60 (36) 0.4111	1/60 (35) 0.9018
	M-Stromal sarcoma	1/60 (30) 0.7169	0/60 (33) 1.0000	1/60 (34) 0.7842	1/60 (35) 0.7909	0/60 (35) 1.0000
Vagina	B-Haemangioma	0/60 (30) 0.6205	0/60 (33) NC	1/60 (34) 0.5312	0/60 (34) NC	0/60 (35) NC
	M-Leiomyosarcoma	0/60 (30) 0.6205	0/60 (33) NC	1/60 (34) 0.5312	0/60 (34) NC	0/60 (35) NC
Whole Body	B-Haemangioma / M-Haemangiosarcoma	4/60 (33) 0.5596	1/60 (34) 0.9754	4/60 (35) 0.6786	6/60 (36) 0.4252	3/60 (37) 0.8304

Figure 2A: Kaplan-Meier Survival Curves for

Male Mice

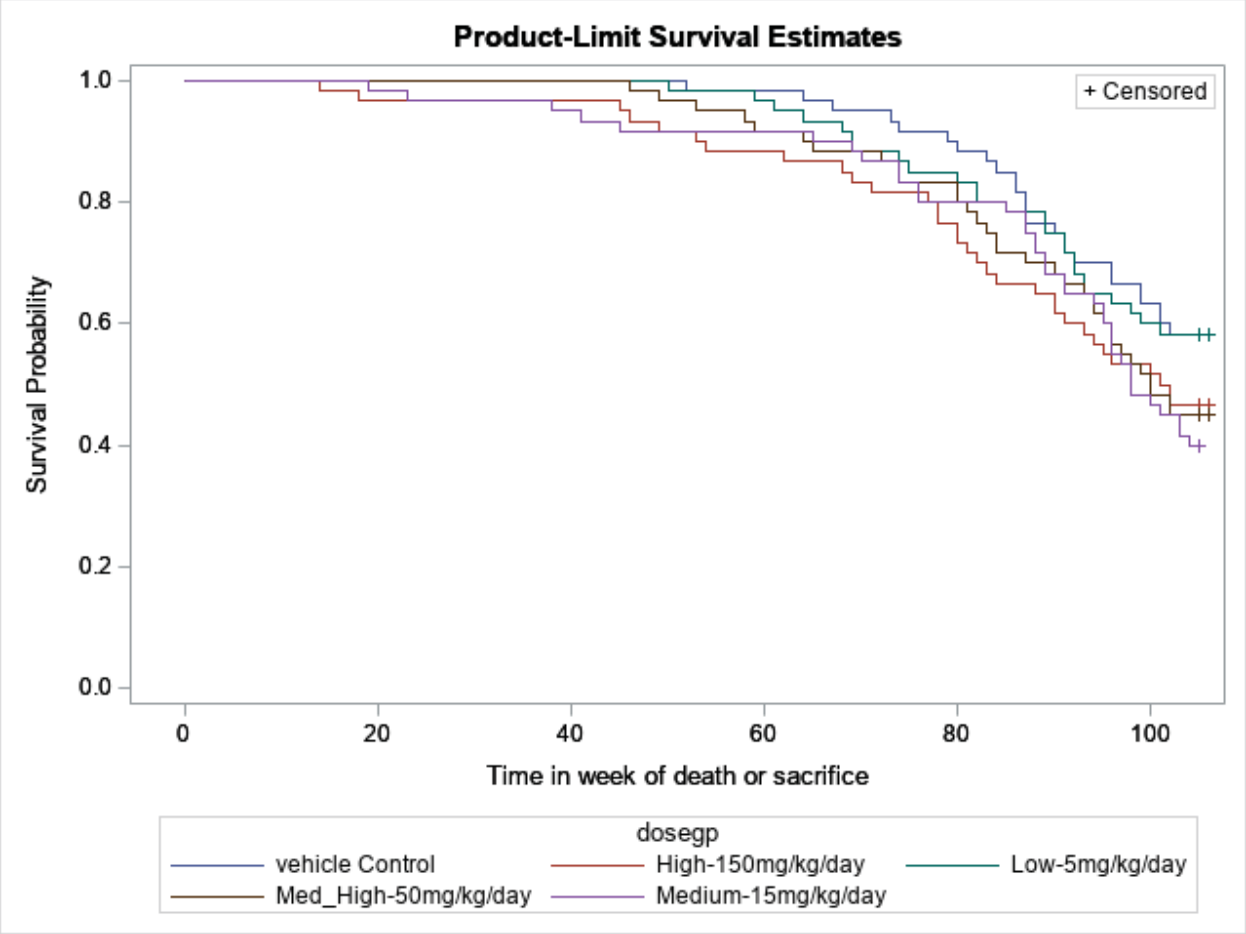
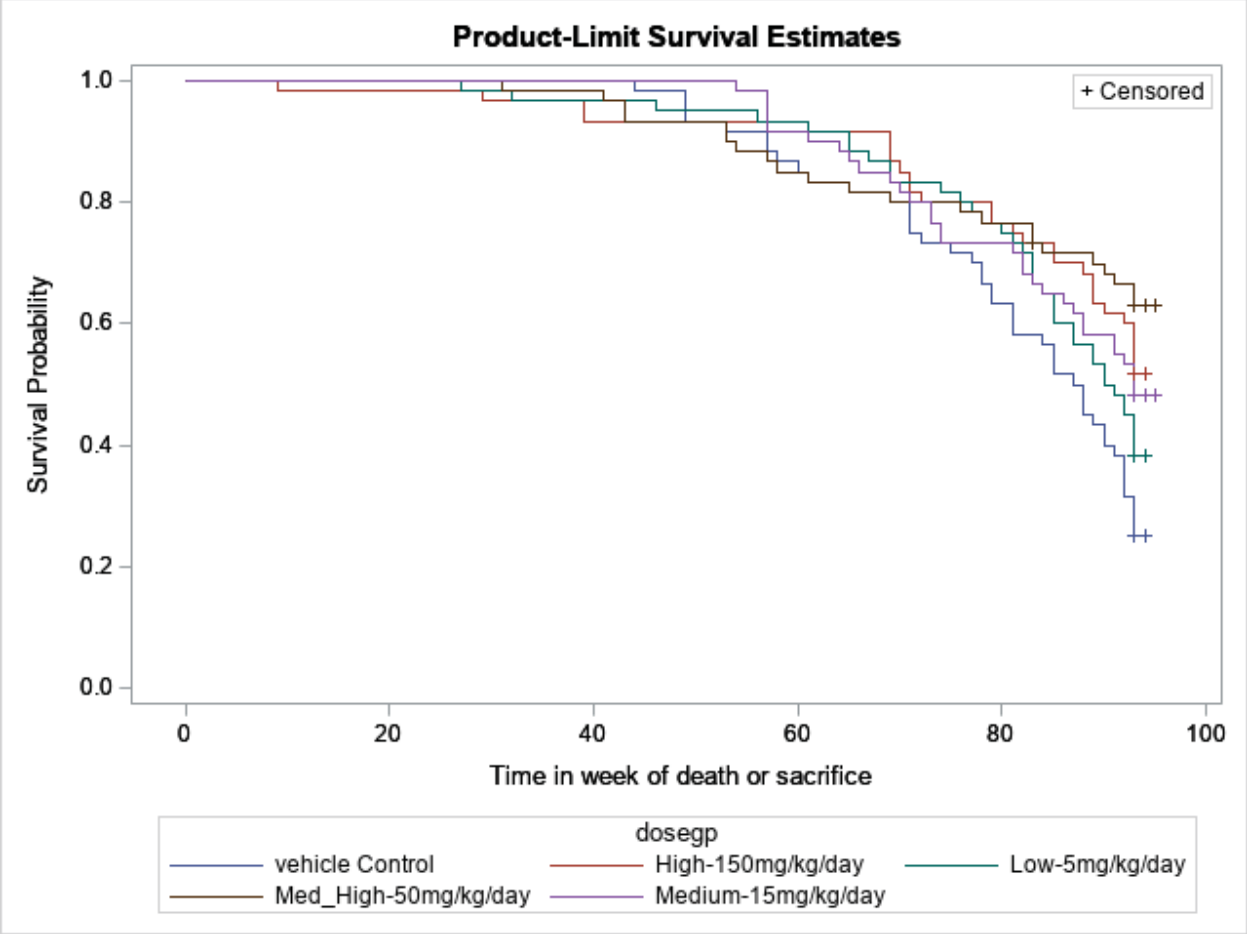


Figure 2B: Kaplan-Meier Survival Curves for
Female Mice



6. References:

1. Bailer AJ, Portier CJ (1988). "Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples." *Biometrics*, 44, 417-431.

2. Bieler, G. S. and Williams, R. L. (1993). "Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity". *Biometrics* 49, 793-801.

3. Gebregziabher M, Hoel D (2009) Applications of the poly-k statistical test to life-time cancer bioassay studies. Hum Ecol Risk Assess 15(5):858{875.

4. Guidance for Industry. Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Statues of Pharmaceuticals (Draft Guidance). U.S. Department of Health and Human Services, Food and Drug Administation, Center for Drug Evaluation and Research (CDER), May 2001.

5. Moon H, Ahn H, Kodell RL, Lee JJ (2003) Estimation of k for the poly-k test with application to animal carcinogenicity studies. Statistics in Medicine 22(16):2619{2636

6. Peto, R., M.C. Pike, N.E. Day, R.G. Gray, P.N. Lee, S. Parish, J. Peto, Richards, and Wahrendorf, "Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments", Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, Annex to supplement, World Health Organization, Geneva, 311-426, 1980.

7. Portier C, Hedges J, Hoel D (1986) Age-speci_c models of mortality and tumor onset for historical control animals in the national toxicology programs carcinogenicity experiments. Cancer Research 46:4372{4378
8. Lin, K.K., and M.A. Rahman (1998), "Overall False Positive Rates in Tests for Linear Trend in Tumor Incidence in Animal Carcinogenicity Studies of New Drugs", Journal of Biopharmaceutical Statistics, with discussions, 8(1), 1-22.

9. Rahman M.A. and Lin K.K, "A comparison of False Positive Rates of Peto and Poly-3 Method For Long Term Carcinogenicity Data Analysis Using Multiple Comparison Adjustment Method Suggested by Lin and Rahman" Journal of Biopharmaceutical Statistics, 18: 949-958, 2008.

10. Tarone RE, "Test for trend in life table analysis", Biometrika 1975, 62: 679-82

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Concur with review.

Office of Clinical Pharmacology Integrated Review

NDA Number	214377
Link to EDR	\\CDSESUB1\EVSPROD\NDA214377\214377.enx
Submission Date	5/20/2020
Submission Type	505(b)(1)
Brand Name	VERQUVO™
Generic Name	Vericiguat
Dosage Form and Strength	2.5 mg, 5 mg, 10 mg film-coated tablets
Proposed Indication	To reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for heart failure or need for outpatient IV diuretics, in adults with symptomatic chronic HF and ejection fraction less than 45%
Applicant	Merck
Associated IND	116743
OCP Review Team	Anusha Ande, Ph.D., Girish Bende, Ph.D., Justin Earp, Ph.D., Jianghong Fan, Ph.D., Yuching Yang, Ph.D., Sudharshan Hariharan, Ph.D.
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1. EXECUTIVE SUMMARY

This clinical pharmacology review is for an original 505(b)(1) new molecular entity (NME) NDA submitted by Merck on May 20, 2020 to the Division of Cardiology and Nephrology (DCN). The Applicant is seeking approval for VERQUVO™ (vericiguat) to reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for HF or need for outpatient IV diuretics, in adults with symptomatic chronic HF and ejection fraction less than 45%. Vericiguat is a stimulator of soluble guanylate cyclase (sGC). HF is associated with impaired synthesis of nitric oxide (NO) and decreased activity of its receptor, sGC. Vericiguat restores the relative deficiency in NO-sGC-cGMP pathway by directly stimulating sGC, independently and synergistically with NO, to augment the levels of intracellular cyclic guanosine monophosphate (cGMP), which may improve both myocardial and vascular function.

The clinical pharmacology program for vericiguat consisted of 28 Phase 1 studies (i.e., single- and multiple-ascending dose, absolute and relative bioavailability, food effect, mass balance, pharmacokinetic (PK) and pharmacodynamic (PD) drug interaction, renal and hepatic impairment, QTc study) complemented by the SOCRATES-REDUCED (Phase 2) and VICTORIA (Phase 3) studies, and population pharmacokinetic (popPK), PK/PD, PK-safety, PK-efficacy, and physiologically-based pharmacokinetic (PBPK) modeling reports. In addition, the submission contains 29 in vitro studies evaluating distribution, metabolism, protein binding, and in vitro metabolic/transporter-based drug interactions. The Applicant is relying on the Phase 3 randomized, placebo-controlled, double-blind, event-driven, multicenter clinical trial (VICTORIA) in adult subjects with symptomatic chronic HF and ejection fraction less than 45% following a worsening HF event. VICTORIA demonstrated a statistically significant effect on its primary endpoint, the time to first occurrence of CV death or HF hospitalization (HR: 0.90, 95%CI: 0.82, 0.98; p = 0.019). Vericiguat treatment resulted in a 10% relative hazard reduction compared to placebo.

Key issues addressed in this review are:

(1) Appropriateness of the proposed dose in specific patient populations (i.e., renal and hepatic impairment)
(2) Appropriateness of the proposed dose when co-administered with gastric pH modifying agents

1.1 Recommendations

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in NDA 214377 to support an approval of vericiguat.

Key review issues with specific recommendations and comments are summarized below:

Review Issues	Acceptable to OCP	Recommendations and Comments

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Pivotal or supportive evidence of effectiveness	☑Yes ☐No ☐N/A	The primary evidence of effectiveness is from one Phase 3 randomized, placebo-controlled, double-blind, event-driven, multicenter clinical trial (VICTORIA) in adult subjects with symptomatic chronic HF and ejection fraction less than 45% following a worsening HF event. VICTORIA demonstrated a statistically significant effect on its primary endpoint, the time to first occurrence of CV death or HF hospitalization (HR: 0.90, 95%CI: 0.82, 0.98; p = 0.019).
General dosing instructions	☑Yes ☐No ☐N/A	The recommended starting dose of vericiguat is 2.5 mg orally once daily with food. Double the dose of vericiguat approximately every 2 weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient.
Dosing in patient subgroups (intrinsic and extrinsic factors)	☑Yes ☐No ☐N/A	• In general, no dose adjustment is necessary in patients based on gender, body weight, race and ethnicity. • No dose adjustment is necessary in patients with estimated glomerular filtration rate (eGFR) ≥15 mL/min and not on dialysis. Vericiguat has not been studied in patients with eGFR <15 mL/min at treatment initiation or in patients on dialysis. • No dose adjustment is necessary in patients with mild and moderate hepatic impairment. Vericiguat has not

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		been studied in patients with severe hepatic impairment. • No dose adjustment is necessary with concomitant medications.
Labeling	☑Yes ☐No ☐N/A	Pending satisfactory agreement with the Applicant
Bridge between the to-be-marketed and clinical trial formulations	☐Yes ☐No ☑N/A	The to-be-marketed formulation is the same as the clinical trial formulation.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of Action

Vericiguat is a stimulator of soluble guanylate cyclase (sGC) resulting in smooth muscle relaxation and vasodilation. Heart failure is associated with impaired synthesis of nitric oxide (NO) and decreased activity of its receptor, sGC. Soluble guanylate cyclase catalyzes synthesis of intracellular cyclic guanosine monophosphate (cGMP), an important signaling molecule that regulates critical physiological processes such as cardiac contractility, vascular tone, and cardiac remodeling. Deficiency in sGC-derived cGMP contributes to myocardial and vascular dysfunction. Vericiguat restores the relative deficiency in this signaling pathway by directly stimulating sGC, independently and synergistically with NO, to augment the levels of intracellular cGMP, which may improve both myocardial and vascular function (***Figure 1***).

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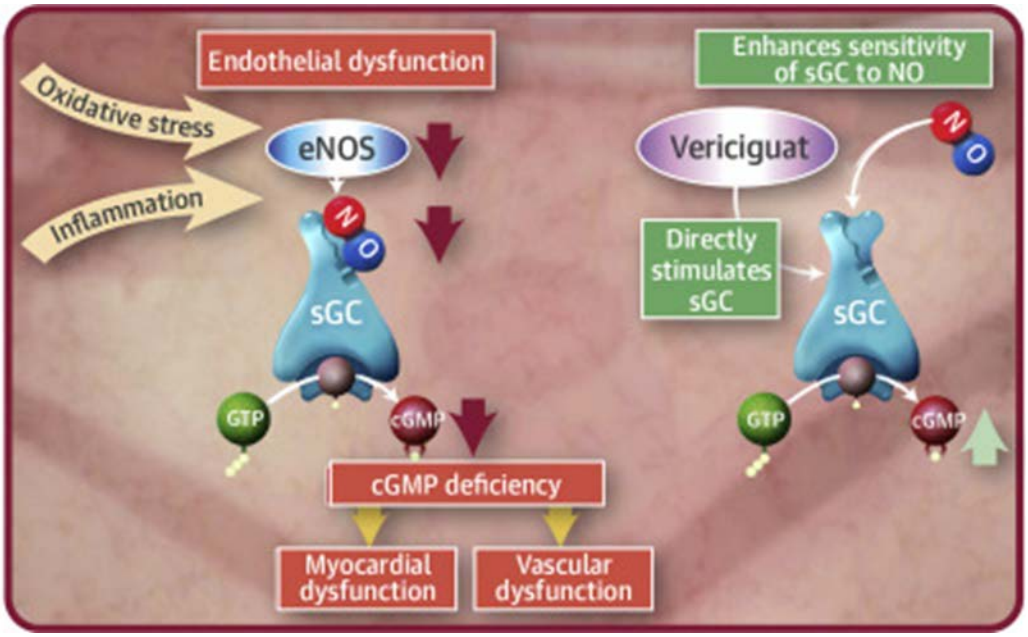
Figure 1 Mechanism of Action[1]



Absorption

The absolute bioavailability of vericiguat is 93% when taken with food. Similar results were obtained when vericiguat was administered orally as a crushed tablet in water.

Effect of Food

Administration of vericiguat 10 mg with a high-fat, high-calorie meal delays median T_{max} from about 1 hour (fasted) to about 4 hours (fed), reduces PK variability, and increases vericiguat AUC by 44% and Cmax by 41% as compared with administration in the fasted state. Similar results were obtained when vericiguat was administered with a low-fat, high-carbohydrate meal.

Distribution

The mean steady-state volume of distribution of vericiguat is approximately 44 L in healthy subjects. Protein binding (primarily to serum albumin) of vericiguat is about 98%.

Elimination

Clearance of vericiguat is 1.6 L/h in healthy subjects. The terminal half-life of vericiguat is approximately 20 hours in healthy subjects and 30 hours in patients with heart failure.

Metabolism

[1] Armstrong et al. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy and Safety of the Oral Soluble Guanylate Cyclase Stimulator (The Victoria Trial). JACC: HEART FAILURE VOL. 6, No. 2, 2018: 96-104.

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Vericiguat primarily undergoes glucuronidation by UGT1A9 and to a lesser extent by UGT1A1 to form an inactive N-glucuronide metabolite. CYP-mediated metabolism is a minor clearance pathway (<5%).

Excretion

Following oral administration of radiolabeled vericiguat after a 10-hour overnight fast to healthy subjects, approximately 53% of the dose was excreted in urine (primarily as inactive metabolite M-1) and 45% in feces (primarily as unchanged).

Intrinsic factors

No clinically significant differences in the pharmacokinetics of vericiguat were observed based on age, sex, race/ethnicity (Black, White, Asian, Hispanic), body weight, or mild to moderate hepatic impairment (Child-Pugh A to B).

In the dedicated renal impairment (RI) study, subjects with moderate and severe RI had 73% and 143% higher mean vericiguat AUC respectively, compared to their matched healthy controls. No effect on vericiguat peak plasma concentration was observed. The popPK analysis in subjects with heart failure with reduced ejection fraction (HFrEF) showed no meaningful effect of eGFR on vericiguat exposure after accounting for body weight. The effect on exposure of vericiguat from popPK analyses of Phase 2 and 3 studies is smaller than the effect observed in the dedicated renal impairment study. The reasons for differences in impact of renal function between dedicated study and popPK analyses is not exactly clear, but could plausibly be because the dedicated renal impairment study was conducted in a well-controlled setting compared to Phase 2 and 3 studies with potential variability with regards to food and concomitant medications.

The effect of eGFR <15 mL/min, dialysis, or severe hepatic impairment (Child-Pugh C) on vericiguat pharmacokinetics has not been studied.

Drug Interaction Studies

Clinical Studies

After fasted administration of vericiguat in a dedicated study, omeprazole decreased the vericiguat mean AUC by 32.2% and mean C_{max} by 49.6% and increased median T_{max} from 0.98 to 2.5 h. Antacid (aluminum hydroxide /magnesium hydroxide combination) decreased the vericiguat mean AUC and C_{max} by a similar extent (-27.1% and -45.7%, respectively) and increased median vericiguat T_{max} from 0.98 to 3.5 h. No clinically significant differences on vericiguat pharmacokinetics were observed with co-administration of drugs increasing gastric pH (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) in heart failure patients, when administered with food based on popPK analysis from Phase 2 and 3 studies, indicating that the effect of food overrules that of the pH.

No clinically significant differences on vericiguat pharmacokinetics were observed with coadministration of mefenamic acid (UGT1A9 inhibitor), ketoconazole (strong CYP3A and P-

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gp inhibitor), rifampin (UGT, CYP and P-gp inducer), digoxin (P-gp substrate), warfarin, aspirin, sildenafil, or the combination of sacubitril/valsartan in healthy subjects. No clinically significant differences on vericiguat pharmacokinetics were predicted with co-administration of atazanavir (UGT1A1 inhibitor) based on PBPK analysis.

No clinically significant differences on the pharmacokinetics of midazolam (CYP3A substrate), digoxin (P-gp substrate), warfarin, sildenafil, or the combination of sacubitril/valsartan were observed when coadministered with vericiguat in healthy subjects.

In Vitro Studies

Cytochrome P450 (CYP) enzymes: Vericiguat is not an inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4 and is not an inducer of CYP1A2, 2B6 or 3A4.

Uridine diphosphate (UDP)-glucuronosyl transferase (UGT) enzymes: Vericiguat is not an inhibitor of UGT1A1, 1A4, 1A6, 1A9, 2B4, or 2B7.

Transporter Systems: Vericiguat is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) but is not a substrate of organic cation transporter (OCT1) or organic anion transporting polypeptides (OATP1B1 and OATP1B3). Vericiguat is not an inhibitor of P-gp, BCRP, BSEP, OATP1B1/1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2K.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

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

2.2.2 Therapeutic individualization

- No dose adjustment is needed in patients based on age, body weight, gender, race/ethnicity.
- No dose adjustment is recommended in patients with eGFR ≥15 mL/min and not on dialysis. Vericiguat has not been studied in patients with eGFR <15 mL/min at treatment initiation or on dialysis.
- No dose adjustment is recommended in patients with mild or moderate hepatic impairment (e.g., Child-Pugh A or B). Vericiguat has not been studied in patients with severe hepatic impairment (e.g., Child-Pugh C).
- Vericiguat has a low DDI risk and can be safely administered with drugs commonly prescribed to HF patients, including digoxin, warfarin, acetylsalicylic acid, sacubitril/valsartan, and organic nitrates. Concomitant administration of UGT inhibitors and rifampin (UGT, P-gp and CYP inducer) does not have a clinically meaningful effect on the pharmacokinetics of vericiguat.

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2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The clinical pharmacology section of the proposed label was updated to reflect the current Guidance on Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products.

The following edits are suggested in section 12:

- Drug Interaction Studies: Include a summary list of studied drugs without a clinically significant impact on meaningful PD endpoint instead of a [redacted] (b) (4) .
- Pharmacokinetics: Include exposure for one dosage since there is no therapeutic drug monitoring (TDM) for this drug. [redacted] (b) (4)
- [redacted] (b) (4) organ impairment studies [redacted] (b) (4) using the data from both the dedicated studies and popPK analyses. The effect on exposure of vericiguat from popPK analyses of Phase 2 and 3 studies is smaller than the effect observed in the dedicated renal impairment study, given the dedicated renal study was conducted in a well-controlled setting compared to Phase 2 and 3 studies with potential variability with regards to food and concomitant medications.
- [redacted] (b) (4) PPI data [redacted] (b) (4) using the data from both the dedicated study and popPK analysis. The effect on the exposure of vericiguat was more pronounced in the dedicated study because it was conducted in the fasted state.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Vericiguat is a soluble guanylate cyclase (sGC) stimulator that was co-developed by Merck and Bayer for the treatment of chronic heart failure (NYHA class II-IV) in adults with reduced left ventricular ejection fraction (LVEF <45%) in addition to standard of care to reduce the risk of cardiovascular death and heart failure hospitalization. Merck serves as the marketing authorization holder in the US and holds sponsorship of IND 116743 under which the pivotal trial was conducted.

Vericiguat was granted Fast Track Designation in 2014. An EOP2 meeting was held in 2015 after completion of a phase 2b study (Study 15371- SOCRATES-REDUCED). At the meeting, the Division of Cardiology and Nephrology agreed that a single pivotal trial would be sufficient to submit a marketing application with a p-value substantially <0.05, and the mortality component trending in a positive direction. The global clinical trial called, VerICiguaT glObal study in patients with heart failure and Reduced ejectIon frAction (VICTORIA) commenced in

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2016 and concluded in 2019. Topline results were shared at a meeting conducted on February 3, 2020. The trial met its primary endpoint according to Applicant's analyses. The NDA was submitted in May 2020 and was granted priority review status.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Vericiguat is a stimulator of soluble guanylate cyclase (sGC) resulting in smooth muscle relaxation and vasodilation. Progression of HF has been linked to impairments in the NO-sGC-cGMP pathway. Vericiguat restores the relative deficiency in this signaling pathway by directly stimulating sGC, independently and synergistically with NO, to augment the levels of intracellular cGMP, which may improve both myocardial and vascular function.
Cardiac Electrophysiology	There was no evidence of proarrhythmic risk in an in vitro assessment of vericiguat or its major N-glucuronide metabolite. No inhibition of cardiac ion channels (hERG, hNav1.5, or hKvLQT1/mink) was observed at substantial multiples of their unbound Cmax values at the recommended target dose of 10 mg. In a dedicated QT study in patients with stable coronary artery disease, administration of vericiguat 10 mg at steady-state did not cause large mean increases (i.e. >20 msec) in the QT interval. Due to non-optimal study design, the study was not adequate to rule out small increase of >10 msec. (See QT-IRT review for details)
General Information	
Bioanalysis	Vericiguat concentrations in plasma samples were determined using a validated bioanalytical assay (Refer Appendix 4.1). The samples were analyzed using a liquid chromatography and tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) of 0.2 ng/mL.
Dose proportionality	Pharmacokinetics is dose-proportional from 2.5 mg to 10 mg after single dose and once daily dosing of vericiguat tablets (fed) in healthy subjects. In subjects with HFrEF (SOCRATES-REDUCED and VICTORIA), vericiguat exposure was slightly less than dose proportional, such that those who received a 10 mg dose had a 73% higher exposure compared to those who received 5 mg who had 84% higher exposure compared to those who received a 2.5 mg dose.

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Accumulation	Vericiguat accumulates in plasma up to 155-171% and reaches steady-state after approximately 6 days.
Drug exposure (variability) at steady state following the therapeutic dosing regimen	Vericiguat steady-state mean (CV%) Cmax is 350 mcg/L (29%) and AUC is 6,680 mcg.h/L (33.9%) following administration of vericiguat 10 mg in patients with heart failure.
Absorption	
T_{max}	The median T_{max} of vericiguat is 2 hours (1-4.5) in fasted state and 4.5 hours (3 -7.9) in fed state following administration of 10 mg tablet.
Absolute bioavailability	The absolute bioavailability of vericiguat is 93% when taken with food. Similar results were obtained when vericiguat was administered orally as a crushed tablet in water.
Food Effect	Administration of vericiguat with a high-fat, high-calorie meal delays Tmax from about 1 hour (fasted) to about 4 hours (fed) and increases vericiguat AUC by 44% and Cmax by 41% following administration of vericiguat 10 mg as compared with the fasted state. Similar results were obtained when vericiguat was administered with a low-fat, high-carbohydrate meal.
Distribution	
Volume of distribution	The mean steady-state volume of distribution of vericiguat is approximately 44 L in healthy subjects.
Protein binding	Protein binding of vericiguat is about 98%, primarily to serum albumin.
Substrate of transporter systems	Vericiguat is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) but is not a substrate of organic cation transporter (OCT1) or organic anion transporting polypeptides (OATP1B1 and OATP1B3).
Elimination	
Half-life	Clearance of vericiguat is 1.6 L/h in healthy subjects. The terminal half-life of vericiguat is approximately 20 hours in healthy subjects and 30 hours in patients with heart failure.
Metabolism	
Primary metabolizing enzymes	Vericiguat primarily undergoes glucuronidation by UGT1A9 and UGT1A1 to form an inactive N-glucuronide metabolite. CYP-mediated metabolism is a minor clearance pathway (<5%).

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Inhibitor/Inducer	Vericiguat is not an inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4 and is not an inducer of CYP1A2, 2B6 or 3A4. It is not an inhibitor of UGT1A1, 1A4, 1A6, 1A9, 2B4, or 2B7.
Excretion	
Primary excretion pathways	Following oral administration of radiolabeled vericiguat after a 10-hour overnight fast to healthy subjects, approximately 53% of the dose was excreted in urine (primarily as inactive metabolite M-1) and 45% in feces (primarily as unchanged).

3.3 Clinical Pharmacology Questions

3.3.1. To what extent does the available clinical pharmacology program provide supportive evidence of effectiveness?

The primary evidence of effectiveness of vericiguat is based on a multicenter, randomized, parallel-group, placebo-controlled, double-blind, event-driven Phase 3 study VICTORIA in subjects with HFrEF. From a pharmacodynamic standpoint, the effect on N-terminal peptide sequence of the brain natriuretic peptide prohormone (NT-proBNP), a biomarker indicative of ventricular wall stretch, was studied in the Phase 2 study, SOCRATES-REDUCED, which formed the basis for selection of dosing regimen for VICTORIA. SOCRATES-REDUCED used a parallel-group design to compare four different dose regimens and one placebo arm to find the optimal dose for the Phase 3 study. The study had three phases: 1) a screening and randomization phase of 0 to 28 days duration, 2) a study drug treatment phase of 12 weeks duration, and 3) a follow-up phase within 30±5 days. Subjects stabilized after hospitalization or IV diuretic treatment for worsening chronic heart failure with reduced EF were eligible for enrollment in the study. Subjects were randomized to one of the following treatment arms: 1) placebo and sham titration, 2) 1.25 mg and sham titration, 3) 2.5 mg and sham titration, 4) 2.5 mg up-titrated to 5 mg after 14 days, and 5) 2.5 mg up-titrated to 5 mg after 14 days and to 10 mg after 28 days. Subjects took the study drug or placebo once daily in the morning with food. The primary variable was change from baseline to Week 12 in log-transformed NT-proBNP.

In SOCRATES-REDUCED, QD dosing with vericiguat for 12 weeks was well tolerated and provided sufficient evidence of a dose-response relationship for reduction in NT-proBNP, with clinically significant reductions in the highest dose group (titration from 2.5 to 10 mg) (see ***Table 1***). Consistent with these biomarker changes, favorable trends in clinical events (composite of CV death and HF hospitalization, and physician-reported disease severity (NYHA Class) were seen.

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Table 1 Change from baseline in log-transformed NT-proBNP at Visit 5

Treatment	Back transformed GMR [90%CIs]	p-value (t-test one-sided)
1.25 mg	1.02 [0.81, 1.27]	0.544
2.5 mg	0.96 [0.77, 1.20]	0.384
2.5 to 5 mg	0.93 [0.73, 1.18]	0.304
2.5 to 10 mg	0.78 [0.61, 1.00]	0.048
Pooled Comparison	0.89 [0.73, 1.08]	0.151

Source: [Ref. 5.3.5.1: P002MK1242: Table 9-7]

Based on these results, the pivotal VICTORIA study was designed to evaluate the effects on primary endpoint, i.e., whether vericiguat is superior to placebo on a background of guideline-directed medical therapy for HF in increasing the time to the first occurrence of the composite endpoint of CV death or HF hospitalization in HFrEF subjects following a worsening HF event. Male and female subjects aged 18 years or older with chronic HF with reduced ejection fraction (<45%), elevated levels of natriuretic peptides, and a previous HF decompensation were enrolled in this trial. All subjects were required to be clinically stable at the time of randomization. Subjects were randomized within 30 days of the screening visit and within 6 months after hospitalization for HF or within a time period of up to 3 months if treatment with intravenous (IV) diuretic (without hospitalization) was used as an indicator for HF decompensation. The study design included 2 treatment groups (vericiguat and placebo) and used a titration regimen starting with 2.5 mg vericiguat or matching placebo followed by 2 dose doublings in 2-week intervals to reach the 10-mg target dose, dependent on the subject's tolerance determined by systolic blood pressure (SBP) and symptoms. Dose decreases were allowed as determined by SBP, symptoms of hypotension, or at the discretion of the investigator. The success criterion for the primary endpoint was met and vericiguat treatment resulted in a 10% relative hazard reduction in the first event of confirmed CV death or HF hospitalization compared with placebo (HR 0.90 [95% CI, 0.82- 0.98]; p=0.019). Please refer to the clinical and statistical review for the detailed primary efficacy analysis.

With regard to the effect on NT-proBNP in VICTORIA, there was a decreasing trend observed for NT-proBNP levels with time throughout the study duration. The magnitude of effect on NT-proBNP levels was relatively higher for the subjects on vericiguat compared to those on placebo. It is important to highlight that the subjects in this study received treatment on the background of standard of care. This decreasing trend in NT-proBNP levels was consistent across all four quartiles of baseline NT-proBNP up to week 32. Since VICTORIA was an event drive study,

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there was a limited data available after Week 32 to conduct comparative assessment with placebo group. **Table 2** indicates that the treatment effect on NT-proBNP levels were preserved until Week-32.

Table 2 Geometric Ratio for NT-proBNP as Change from Baseline compared to Placebo (by quartiles of NT-proBNP levels at baseline)

Quartiles* (V: 2419; P: 2386)		Week-16 (V: 2052; P: 2061)	Week-32 (V: 2012; P: 2002)
Vericiguat / Placebo	Q1	0.922	0.900
	Q2	0.888	0.905
	Q3	0.840	0.885
	Q4	0.930	0.897
	ALL	**0.898**	**0.888**

**by quartiles of NT-proBNP levels at baseline; Sample Size: V: for Vericiguat and P: for Placebo*

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed titration dosing regimen with a starting dose of 2.5 mg, an SBP guided titration of dose doublings approximately every two weeks, and a targeted therapeutic dose of 10 mg once daily is acceptable to reduce the risk of cardiovascular death and HF hospitalization following a hospitalization for heart failure or need for outpatient IV diuretics, in adults with symptomatic chronic HF and ejection fraction less than 45%.

Rationale for Phase 3 Dose Selection (Phase 2 study Findings)

In SOCRATED-REDUCED, vericiguat was well tolerated in subjects that were started on a 2.5 mg dose in addition to standard therapy for HF. Exploratory analysis revealed a relationship between higher vericiguat exposure (C_{max}) and decreases in SBP after the first dose, but no exposure-response relationship between C_{max} and change in SBP was observed at steady state indicating an adaptation to the hemodynamic effects of vericiguat over time (**Figure *2***). Therefore, in VICTORIA, subjects with HFrEF were initiated on the 2.5 mg dose.

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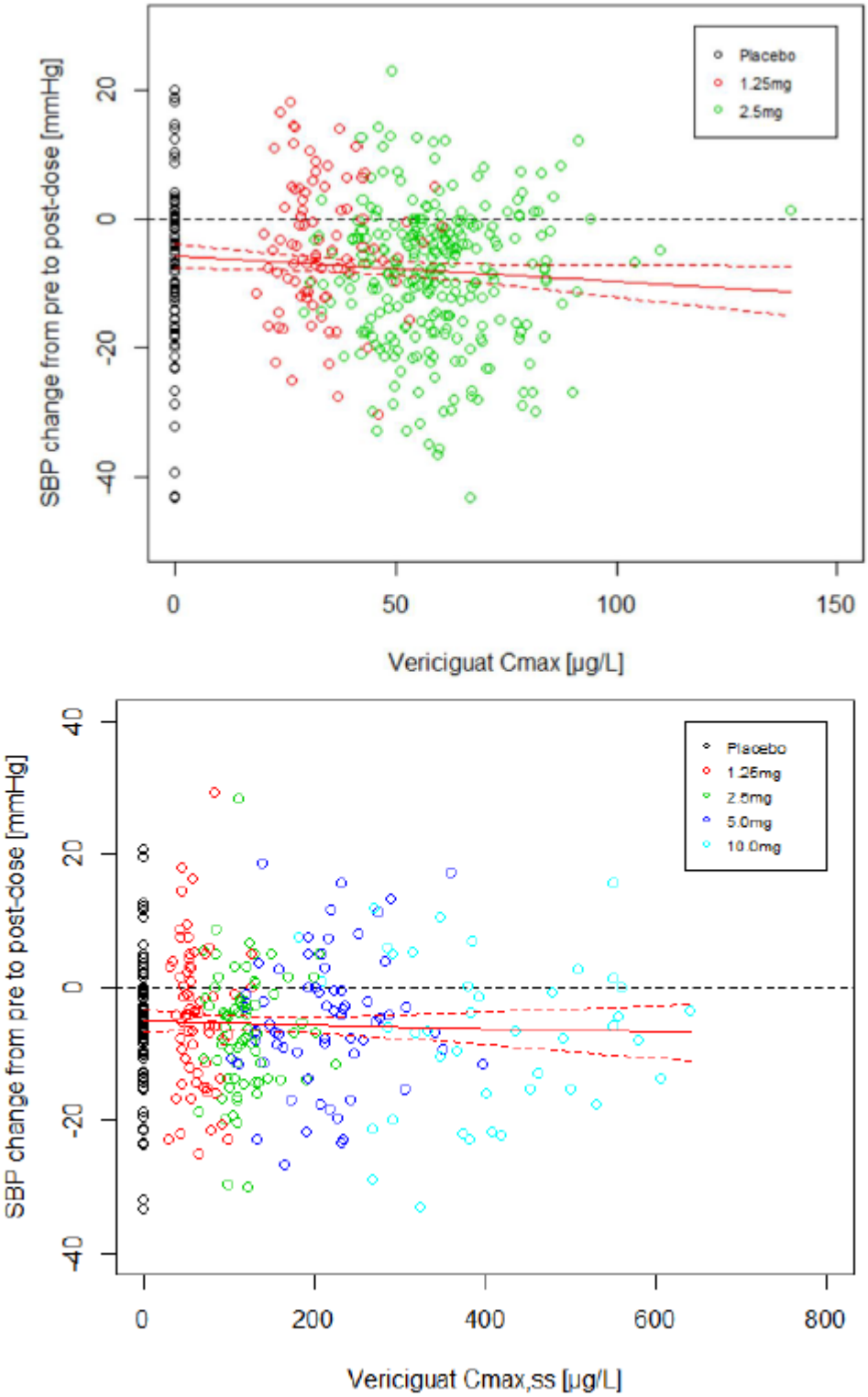
Figure 2 Correlation of vericiguat peak concentrations (C_{max}, $C_{max,ss}$) with pre- to post-dose change of SBP at visit 1 (first dose, upper panel) and visit 4 (after 8 weeks, lower panel)



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Source: [Ref. 5.3.3.5: 05GJCP: Figure 2.4 2]

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 3 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 ($p = 0.528$)

[Source: Ref. 5.3.3.5: 05GJCP: Table 11 6]

A direct relationship between vericiguat plasma concentrations and hemodynamic effects on parameters such as heart rate (HR) and BP were observed in healthy subjects. HR increases were still observed after 1 week of vericiguat treatment indicating that pharmacodynamic steady state is not reached by this time. Therefore, a titration interval of about 14 days was included into the titration regimen of SOCRATES-REDUCED and VICTORIA.

Further, titration to the 10 mg dose provided the largest decrease in NT-proBNP and majority of subjects (72%) in SOCRATES-REDUCED reached the 10 mg dose following the SBP guided titration. These results formed the basis for selection of 10 mg as the target dose for VICTORIA.

Confirmation of Dose Titration Regimen and Target Dose in VICTORIA

The SBP guided titration regimen was first examined with data from SOCRATES-REDUCED where an adaptation to the effect of vericiguat on pre- to post-dose SBP was observed as previously mentioned. The titration regimen was then confirmed in VICTORIA, where a similar adaptation was observed. In the exposure-SBP analysis, there was a small but statistically significant correlation between higher vericiguat exposures (C_{max}) and decrease in baseline in SBP 2h post-dose on Day 1. However, there was no relationship between vericiguat exposure and change in SBP from baseline during the day 14 visit and through the remainder of the trial. Furthermore, in subjects on the 2.5 mg dose during the first 14 days of treatment, there was no meaningful exposure-response relationships for symptomatic hypotension or syncope. Together, these results demonstrate that the 2.5 mg dose is a suitable starting dose for vericiguat in subjects with HFrEF.

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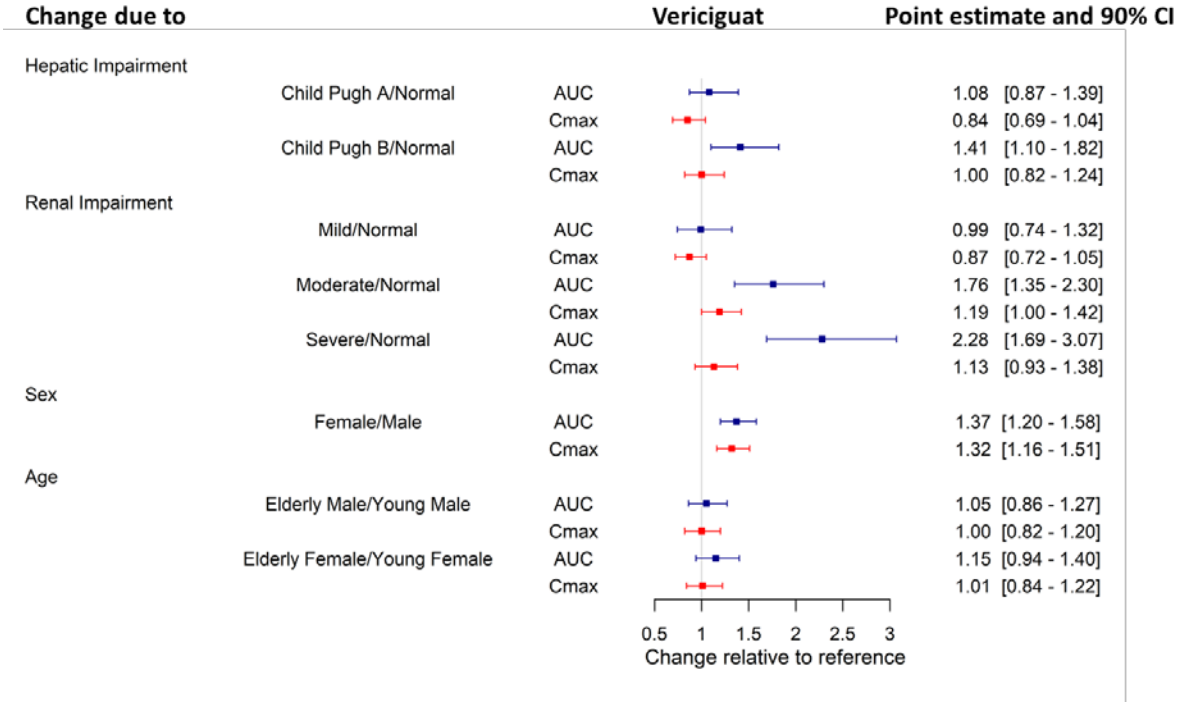
In VICTORIA, a similar proportion of subjects in each treatment group were titrated to the 10-mg target dose at some point in the study (81.9% in the vericiguat group and 84.1% in the placebo group). The appropriateness of this dosing regimen was supported by the significant risk reduction in the composite endpoint of the first event of CV death or HF hospitalization, as well as a favorable safety profile. Taken together these data demonstrate that two dose doublings in intervals of approximately 2 weeks from a starting dose of 2.5 mg vericiguat to a target dose of 10 mg is appropriate for subjects with HFrEF.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No. Dose adjustment is not necessary based on intrinsic factors such as body weight, race, age, sex, mild to severe renal impairment, or mild to moderate hepatic impairment. The effect of intrinsic factors on the PK of vericiguat from the dedicated studies is shown in **Figure *3***.

Figure 3 Pharmacokinetics of Vericiguat in Specific Populations



Body weight

Body weight is the main intrinsic factor influencing vericiguat exposure. In the popPK analyses in subjects with HFrEF, body weight was a statistically significant covariate on both apparent clearance and volume of distribution. 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 body weight > 90 kg, compared to subjects with HFrEF with a body weight between 60 to 90 kg. With respect to efficacy in VICTORIA, a subgroup analysis showed that body weight had no effect on the primary composite endpoint. With respect to

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safety, there was no meaningful exposure-response for safety events of clinical interest (symptomatic hypotension and syncope) across the range of exposures in VICTORIA. Therefore, the effect of body weight on vericiguat exposure is not clinically meaningful.

Race

Vericiguat exposure (AUC and C_{max}) in healthy Asian subjects was about 70 and 80% higher, respectively, when compared to Caucasians. The difference was reduced to about 38% (AUC_{norm}) and 45% ($C_{max,norm}$) when corrected for body weight. In subjects with HFrEF, however, race/ethnicity was not a statistically significant covariate in the popPK analysis.

Age and Sex

Geometric mean C_{max} and AUC values were greater (32% and 37%, respectively) in female subjects relative to male subjects with similar relative changes across both age subgroups (young, 18-45 years; elderly, ≥ 65 years), in the dedicated study. These observed differences in C_{max} and AUC were diminished upon body-weight normalization of the PK parameters in the young and elderly subjects, indicating that body weight drives most of the exposure difference between men and women. No age-related difference in C_{max} was observed between the young subjects and elderly subjects ≥ 65 years. An increase in AUC of about 15% was seen when comparing elderly female vs. young female subjects.

Though sex 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.

Renal Impairment

In the dedicated renal impairment study, exposures were not affected in subjects with mild renal impairment. In subjects with moderate and severe renal impairment, the mean AUC of vericiguat was increased by 76% and 128%, respectively and the mean C_{max} was increased by 19% and 13%, compared to their matched healthy subjects. VICTORIA enrolled patients with all degrees of renal impairment patients (n= 505 with eGFR ≤ 30 mL/min, n= 2118 with 30 – 60 mL/min, n= 2333 with >60 mL/min). PopPK analysis in subjects with HFrEF showed eGFR had no clinically meaningful effect on vericiguat exposures. Vericiguat exposure was slightly higher in subjects with HFrEF with moderate (13%) and severe (20%) renal impairment compared to subjects with HFrEF with a normal renal function. This effect is smaller than the effect observed in the dedicated renal impairment study. The reasons for differences in impact of renal function between dedicated study and popPK analyses is not exactly clear but could plausibly be because the dedicated renal impairment study was conducted in a well-controlled setting compared to Phase 2 and 3 studies with potential variability with regards to food and concomitant medications.

To understand whether any dose-adjustments for impaired renal function was required, the effect of vericiguat on primary composite endpoint in VICTORIA was assessed across eGFR

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subgroups. The proportions of subjects with AEs, SAEs that led to discontinuation were similar between the vericiguat and placebo groups across the eGFR categories (≥15 mL/min without dialysis, data not shown). In addition, from the subgroup analysis of the primary composite endpoint, it is evident that the 95% CIs for the HR overlap across subgroups of eGFR (≥15 mL/min without dialysis) ***Table 4***.

Table 4 Subgroup analysis of the primary composite endpoint by eGFR category

eGFR (total subjects) (ml/min/1.73 m2)	% Total Population	Vericiguat N (%)	Placebo N (%)	HR (95% CI)
≤ 30 (259)	10	143 (55.2)	128 (51.8)	1.06 (0.83, 1.34)
> 30 ≤ 60 (1054)	41.9	392 (37.2)	455 (42.8)	0.84 (0.73, 0.96)
> 60 (1161)	46.2	346 (29.8)	372 (31.7)	0.92 (0.80, 1.07)

N = number of subjects with an event

% = percent of subjects with an event in the subgroup

[Source: Integrated Pharmacokinetic Report]

Furthermore, from a tolerability standpoint, degree of renal impairment did not appear to have a meaningful impact on the proportion of subjects who were titrated to the target dose of 10 mg by visit 4, or on subsequent titrations **Table *5***. Therefore, based on all points considered, no dose adjustment is required in patients with estimated eGFR ≥15 mL/min (without dialysis).

Table 5 Proportions of subjects titrated to 10 mg by Day 56 categorized by eGFR

eGFR (total subjects) (ml/min/1.73 m2)	2.5 mg N (%)	5 mg N (%)	10 mg N (%)
> 60 (1110)	107 (9.6)	174 (15.7)	829 (74.7)
> 30 ≤ 60 (997)	98 (9.8)	192 (19.3)	707 (70.9)
15 ≤ 30 (231)	27 (11.7)	38 (16.5)	166 (71.9)
≤ 15 (3)	1 (33.3)	0 (0)	2 (66.7)

N= number of subjects titrated to the given dose level

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% = percent of subjects titrated to the given dose level in the subgroup

Hepatic Impairment

In the dedicated hepatic impairment study, subjects with moderate hepatic impairment (Child Pugh B) had a 41% higher mean AUC compared to healthy subjects while C_{max} was not affected. Exposures were unaffected in subjects with mild hepatic impairment. These observed differences in vericiguat exposure are not considered clinically relevant. Subjects with severe hepatic impairment were not evaluated in this study.

VICTORIA excluded subjects with severe hepatic insufficiency such as hepatic encephalopathy, but to note, exclusion was not based on Child Pugh classification. Parameters included in the Child Pugh score, such as albumin and bilirubin, were tested as covariates in the SOCRATES-REDUCED/VICTORIA popPK analysis of subjects with HFrEF and they had no effect on vericiguat exposure.

Further, a sub-group analysis for primary efficacy endpoint by hepatic impairment status was conducted by the Applicant following our recommendation. The Applicant proposed to use ALBI grading system, that relies on a score calculated using only albumin and bilirubin values. ALBI score is calculated using the following formula: (log10 bilirubin × 0.66) + (albumin × −0.085), where bilirubin is in µmol/L and albumin in g/L. As with the Child-Pugh score, cutoffs for three grades were determined to best assess prognosis: grade 1 patients (lowest mortality risk) are those with ALBI score ≤ -2.60, grade 2 (intermediate mortality risk) are those with ALBI score > -2.60 and ≤ -1.39, and grade 3 (highest mortality risk) are those with score > -1.39. Applying the ALBI grading system to the VICTORIA population, 63.7% were grade 1, 35.9% were grade 2, and 0.5% were grade 3. Subgroup analysis of the primary composite endpoint was comparable across low risk and intermediate risk ALBI categories **Table *6***.

Table 6 Subgroup analysis of the primary composite endpoint by ALBI grade

	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 [§]
ALBI Score								
≤ -2.6	474/1599 (29.6)	26.1	36.9 (34.0, 40.0)	503/1552 (32.4)	29.1	39.8 (36.8, 43.0)	0.90 (0.80,1.02)	0.947
> -2.6 to < -1.39	398/858 (46.4)	50.5	56.5 (52.2, 61.0)	443/917 (48.3)	55.3	59.1 (54.7, 63.5)	0.92 (0.81,1.06)	
≥ -1.39	8/13 (61.5)	81.4	N/A	6/10 (60.0)	115.8	N/A	0.81 (0.28,2.35)	

[†] Total subjects with an event / time at risk in years.
[‡] Kaplan-Meier estimate and confidence interval at 2 years. N/A: KM estimates and 95% CI cannot be estimated since maximum follow up time in the subgroup was less than 24 months.
[§] 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.
ALBI Score = [Log10(Bilirubin) (µmol/l) × 0.66] + [Albumin (g/l) x(-0.085)]
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).

Source: [P001MK1242: adam-adsl; adbase; adttec]

Further, from a tolerability standpoint, the ALBI grade had no meaningful impact on dose titration (***Table 7***). Although slight difference was observed in the proportion of subjects titrated to 10 mg across low risk and intermediate risk ALBI groups, but majority of the subjects were titrated to 10 mg in both the groups. Therefore, no dose adjustment is required in patients with mild or moderate hepatic impairment.

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Table 7 Proportion of subjects titrated to 10 mg by Day 56 categorized by ALBI grade

ALBI Score	2.5 mg N (%)	5 mg N (%)	10 mg N (%)
≤ -2.60 (1523)	127 (8.3)	227 (14.9)	1169 (76.8)
> -2.60 and ≤ -1.39 (805)	102 (12.7)	176 (21.9)	527 (65.5)
> -1.39 (11)	4 (36.4)	2 (18.2)	5 (45.5)

N= number of subjects titrated to the given dose level

% = percent of subjects titrated to the given dose level in the ALBI grade

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food effect

Intake with a high-fat, high-calorie meal leads to a delay of absorption of vericiguat with a median T_{max} of about 4 h (vs. approx. 1 h in fasted conditions). Food increases vericiguat exposure (AUC) by 19% at a dose of 5 mg and by 44% at 10 mg. Food intake also increased maximum drug concentration (C_{max}) by 9% at 5 mg and by 41% at 10 mg. Vericiguat bioavailability was comparable after administration of 10 mg tablet with a low-fat, high-carbohydrate meal (approximately 400 kcal) or a high-fat, high-calorie meal. In addition, vericiguat shows lower variability when taken with food (standard high-fat meal) (geoCV for AUC_{norm} 35.9% [fasted] vs. 24.8% [fed]). Therefore, vericiguat is recommended to be taken with food consistent with how vericiguat was instructed to be taken with food in VICTORIA and SOCRATES-REDUCED.

PK Interaction Studies

Effects of Other Drugs on the Pharmacokinetics of Vericiguat

The effects of coadministered drugs on the pharmacokinetics of vericiguat have been assessed in clinical drug-drug interaction studies (see **Figure *4***).

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Figure 4 Effects of other drugs on the PK of vericiguat

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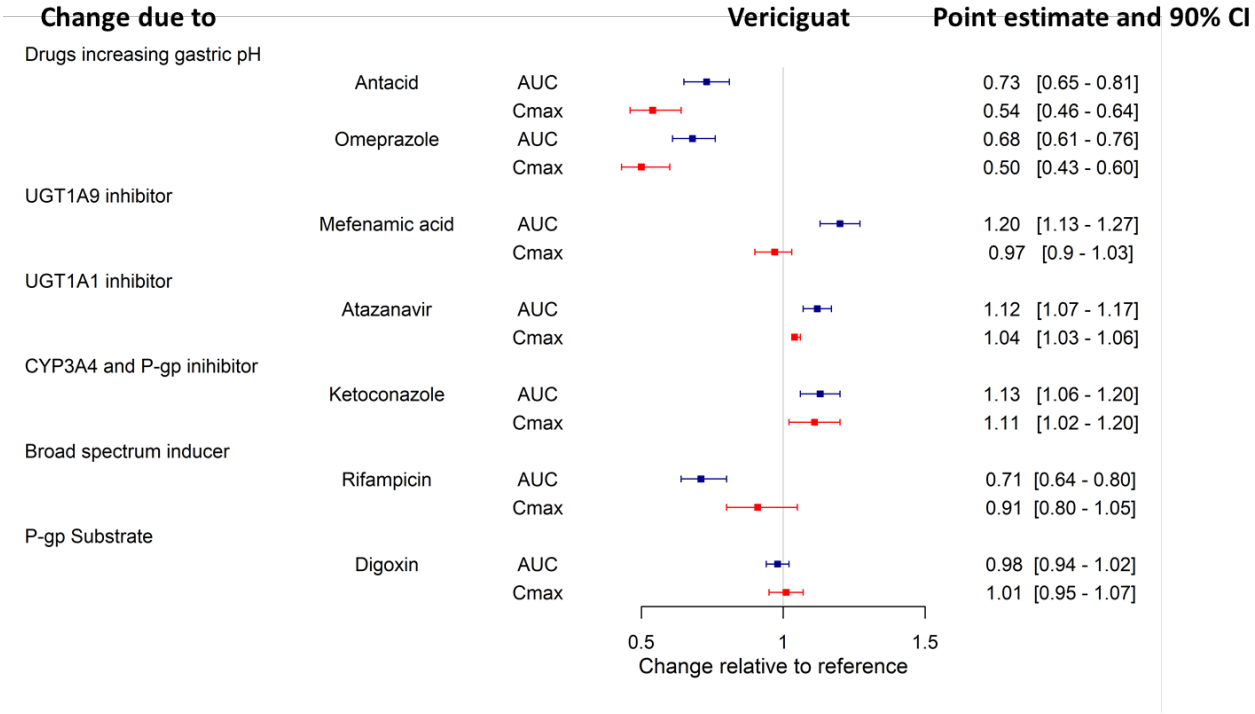

Omeprazole and Antacid Interaction Study

Pre-administration and coadministration of 40 mg omeprazole or coadministration of the aluminum hydroxide/magnesium hydroxide combination antacid (10 mL) with 5 mg vericiguat (fasted) decreased the rate and extent of vericiguat absorption. Omeprazole decreased the vericiguat mean AUC by 32.2% and mean C_{max} by 49.6% and increased median T_{max} from 0.98 to 2.5 h. The antacid decreased the vericiguat mean AUC by 27.1% and mean C_{max} by 45.7% and increased median T_{max} from 0.98 to 3.5 h.

However, this study was conducted under fasting conditions whereas SOCRATES-REDUCED and VICTORIA recommended to take vericiguat together with food. Since food increases gastric pH to 5 – 6, the positive effect of food is expected to mitigate the negative effect of pH on solubility and thus, vericiguat exposure is expected to be less impacted by drugs that increase gastric pH when taken with food. Consistent to this hypothesis, there was no effect on vericiguat exposure in subjects with HFrEF when vericiguat was coadministered with gastric pH modifying agents in the SOCRATES-REDUCED and VICTORIA trials. Therefore, as vericiguat is recommended to be given with food, no dose adjustment is deemed necessary when patients also take drugs that increase gastric pH.

DDI Study with Ketoconazole (CYP3A4 and P-gp inhibitor)

Pre-administration and coadministration of ketoconazole (200 mg bid) had no clinically relevant influence on the PK of a single dose of 1.25 mg vericiguat (approximate increase of 13% in

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vericiguat AUC and 11% in vericiguat C_{max} in healthy subjects with similar $t_{1/2}$). This is consistent with the minor contribution of CYP enzymes to the overall clearance of vericiguat.

DDI Study with Mefenamic acid (UGT1A9 inhibitor)

Pre-administration and coadministration of mefenamic acid (total dose of 2500 mg over 3 days) had no clinically relevant influence on the exposure of a single dose of 2.5 mg vericiguat (about 20% increase in AUC and no change in C_{max} or T_{max}). PBPK analysis indicates that a strong UGT1A9 inhibitor, if available, may lead to greater increase in vericiguat exposure.

DDI Study with Atazanavir (UGT1A1 inhibitor)

Coadministration of atazanavir (400 mg qd) is expected to have no clinically relevant influence on the exposure of 10 mg vericiguat as prospectively evaluated by PBPK modeling (predicted increase in AUC of 12% and C_{max} by 4%) (see section 4.3 for detailed PBPK review).

DDI Study with Rifampicin (a multi-pathway UGT, CYP, and transporter inducer)

Administration of rifampicin (600 mg qd) over 9 days (with 6 days of pre-treatment, on the day of vericiguat administration and on the two days thereafter) decreased the exposure to vericiguat (10 mg tablet) (AUC by 29% and Cmax by 9%), compared with vericiguat alone. However, the decrease in AUC is modest and closer to the observed PK variability of vericiguat.

Effects of Vericiguat on the Pharmacokinetics of Other Drugs
The effects of vericiguat on the pharmacokinetics of coadministered drugs have been assessed in clinical drug-drug interaction studies (see **Figure *5***)

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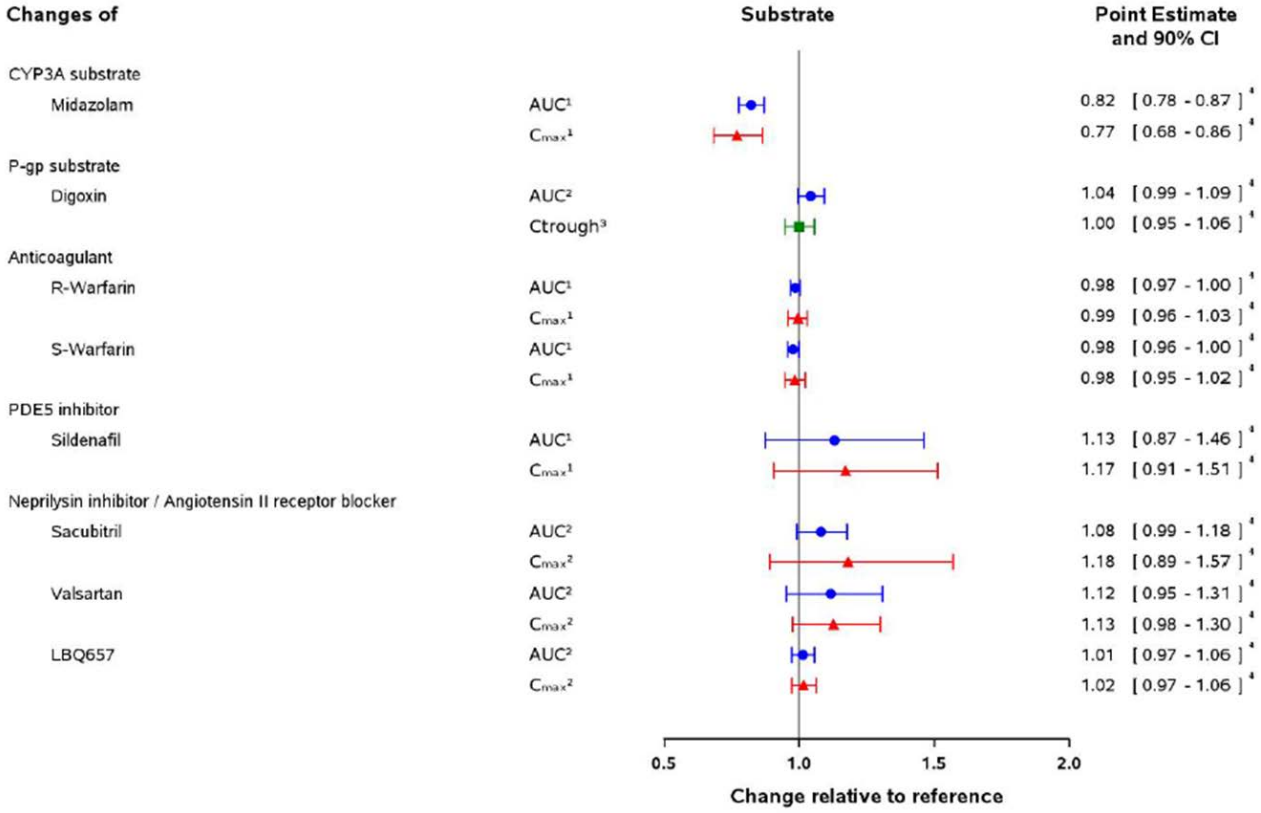
Figure 5 Effects of Vericiguat on the Pharmacokinetics of Other Drugs



DDI study with Midazolam (CYP3A4 index substrate)

Vericiguat administered as 10 mg qd (4-day pre-treatment and coadministration) did not increase the exposure of a single 7.5 mg dose of midazolam (AUC decrease by 18% and Cmax decrease by 23%), indicating that vericiguat is not an inhibitor of CYP3A4. Furthermore, sildenafil is also a CYP3A4 substrate and its pharmacokinetics were not affected by vericiguat coadministration.

DDI study with Digoxin (P-gp index substrate)

Vericiguat did not affect the exposure of digoxin, a commonly prescribed medication in HF, indicating that vericiguat is not an inhibitor of P-gp, consistent with the in vitro P-gp inhibition data. Geometric mean values of the main PK parameters for digoxin $AUC_{\tau,md}$ and $C_{max,md}$ were 18.6 µg*h/L and 1.8 µg/L for digoxin alone and 19.6 µg*h/L and 1.9 µg/L for digoxin with vericiguat, respectively.

PD Interaction Studies

Potential PD interactions were assessed 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 heart failure patients (valsartan/sacubitril).

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Anticoagulants

A single dose of vericiguat 15 mg showed no clinically significant effect on bleeding time or platelet aggregations when given in combination with 500 mg of aspirin. Furthermore, multiple doses of vericiguat 10 mg once daily given together with a single dose of 25 mg warfarin did not have an effect on coagulation (prothrombin time [PT], activities of factors X, VII, II) in comparison to warfarin alone.

Short and long-acting Nitrates

For short-acting nitrates, an interaction study with 0.2 mg nitroglycerin (NTG) in healthy subjects indicated that the effects elicited by NTG on BP (decrease) and HR (increase) are unaffected by the presence of vericiguat. An interaction study with NTG (0.4 mg NTG spray) on top of maintenance treatment with 2.5 to 10 mg vericiguat in subjects with CAD indicated that treatment with NTG spray in combination with vericiguat was generally well tolerated. No statistically significant differences in hemodynamic parameters (SBP, DBP, and HR) between vericiguat and placebo during coadministration with NTG spray were observed.

Vericiguat (up titrated to 10 mg) taken with long-acting nitrates (60 mg isosorbide mononitrate [ISMN]) in subjects with stable CAD showed that the combined treatment was generally well tolerated with similar incidences of treatment-emergent AEs (TEAEs) reported in the vericiguat- and placebo-treated groups during ISMN treatment. SBP and DBP decreases of 2 to 5 mmHg and HR increases of 1 to 2 bpm during coadministration of ISMN with vericiguat were not deemed clinically relevant. In patients with HF, concomitant use with short-acting nitrates was well tolerated, but there is limited experience with long-acting nitrates.

PDE5 inhibitor

Combined treatment of vericiguat 10 mg with single doses of PDE 5 inhibitor sildenafil at doses of 25 mg, 50 mg, and 100 mg was generally well tolerated in healthy subjects. However, vericiguat coadministered with sildenafil resulted in an increased frequency of transient AEs within the system organ class (SOC) of nervous system disorders, most commonly headache and head discomfort, that were predominantly of mild intensity. Coadministration of vericiguat and sildenafil resulted in decreases in seated SBP, DBP, and MAP of less than or equal to 5.4 mmHg when compared with coadministration of placebo and sildenafil. No trend for dose-dependency was observed across the different sildenafil doses. While there were no symptomatic hypotensive events observed, the study was done in healthy subjects and there is limited experience for use of PDE5 inhibitors and vericiguat together, both which act upon the NO-cGMP pathway, in HFrEF patients. Therefore, the use of PDE5 inhibitors with vericiguat is not recommended due to the potential increased risk for symptomatic hypotension.

Sacubitril/Valsartan

Multiple doses of vericiguat 2.5 mg when coadministered with sacubitril/valsartan 97/103 mg in healthy subjects showed no clinically relevant pharmacodynamic interaction (e.g. BP effects <2 mmHg). In VICTORIA, the observed imbalance in symptomatic hypotension and syncope

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between the vericiguat and placebo groups was similar in subjects taking sacubitril/valsartan versus those not taking sacubitril/valsartan with or without vericiguat.

Overall, vericiguat has a low potential as a perpetrator to affect exposure and/or PD effects of drugs commonly prescribed in the heart failure population including digoxin, sacubitril/valsartan and antithrombotics/anticoagulants; No dose adjustment of these drugs is required. Concomitant use with PDE5 inhibitors is not recommended.

3.1.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be marketed formulation?

The immediate release film-coated tablets proposed for commercialization are similar to the tablets used in VICTORIA except for minor modifications of color and embossing (identification numbering/lettering stamped into the tablet). These small changes in the proposed to-be-marketed formulation are not considered to affect the product performance.

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4. APPENDICES

4.1 Summary of Bioanalytical Method Validation

Measurement of vericiguat and M-1 in plasma

Four quantitative liquid chromatography and tandem mass spectrometry (LC-MS/MS) methods for the simultaneous determination of vericiguat and M-1 metabolite in human plasma (i.e., MW 1477, TM1296, ANI 10956, and ANI 10980) was utilized late in the clinical development program. The plasma methods utilized protein precipitation followed by high performance liquid chromatography (HPLC) with tandem mass spectrometric detection, with quantitation being achieved by weighted linear regression using stable isotope-labelled internal standards (ISTD).

Successful cross validation of vericiguat human plasma methods MW 1477 (utilized at Bayer) and TM 1296 (utilized at [redacted] (b) (4)) using sixty-three (63) human plasma study samples has been performed. The mean deviation in sample results between the two methods/labs was less than 3% with only 2 samples deviating more than 10% (-10.10 and -15.31%). Furthermore, a successful cross validation of the vericiguat human plasma methods TM 1296 and ANI 10956 (utilized at [redacted] (b) (4)) using thirty-six (36) human plasma study samples and 6 replicates each of the low, medium and high QC samples spiked by [redacted] (b) (4) is reported. The mean deviation in study sample results between the two methods/labs was less than 2% with only 3 samples deviating more than 10% (-12.39%, 17.97 and -13.14%). All spiked QC sample results met the acceptance criteria, all QC results being within a bias of 11% and a precision of less than 4.0%. Cross validation of ANI 10980 was not performed because this method belongs to the same site ([redacted] (b) (4)) as that of ANI 10956.

The LC-MS/MS methods were validated in compliance with the standards set forth in the FDA Bioanalytical Method Validation guidance. Summary of the validation parameters are presented in ***Table 8***.

Table 8 Summary Review of vericiguat plasma assays

Bioanalytical method validation report	Study reports: 05DGG3, 05DGHB, 05DGJC
Method description	LC-MS/MS method for the determination of vericiguat in human plasma
Method TM.1296	
Materials used for standard calibration curve and concentration	Control human plasma and vericiguat (BAY 1021189) reference standard.

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	Calibrator Concentrations: 0.2, 0.4, 1, 5, 10, 60, 180, and 200 ng/mL	
Validation assay range	0.2 – 200 ng/mL	
QCs	0.6, 10 and 160 ng/mL	
Regression model and weighting	Linear	
Standard calibration curve performance during accuracy and precision runs	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.5% to 1.83%
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 7.79%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 5 QCs	-6.31to -0.43%
	Inter-batch %CV	≤ 7.30%
Selectivity & matrix effect	Analysis of QC1 samples prepared in 6 different lots of control matrix. Bias ranged from 1.33 to 5.50%	
Interference & specificity	Six lots of control matrix tested. No interference was observed in any of the lots tested	
Hemolysis effect	One lot tested. Blanks, low and high QCs were prepared in this lot. No interference was observed. Low QC bias ranged from -0.333 to -5.67%. High QC bias ranged from -3.75 to 0.625%.	
Lipemic effect	One lot tested. Blanks, low and high QCs were prepared in this lot. No interference was observed. Low QC bias ranged from -10.7 to 1.00%. High QC bias ranged from -0.625 to 3.13%.	
Dilution linearity & hook effect	1000 ng/mL tested (n=6) with a 10-fold dilution factor. Mean bias was -11.4%, CV 2.44%	

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Bench-top/process stability	91-hour bench-top stability for Low and High QC samples was established. Mean % bias was 2.36 and -2.19 for the low and high QCs, respectively. Precision (n=6) was 8.70 and 7.64% CV for the low and high QCs, respectively.	
Freeze-Thaw stability	Low and high QC samples were prepared, stored at -80°C and subjected to five freeze-thaw cycles. Mean % bias was determined to be -10.1 and -3.65 for the low and high QCs, respectively. Precision CV, (n=6) was 3.97 and 3.95% for the low and high QCs, respectively.	
Long-term storage	Low and high QC samples were prepared and stored at -20°C and -80°C. Stability at -20°C was established for 433 days. Stability at -80°C was established for 457 days.	
Method ANI 10956		
Materials used for standard calibration curve and concentration	Control human plasma and vericiguat (BAY 1021189) reference standard. Calibrator Concentrations: 0.2, 0.4, 4, 20, 40, 80, 160, and 200 ng/mL	
Validation assay range	0.2 – 200 ng/mL	
QCs	0.6, 10 and 150 ng/mL	
Regression model and weighting	Linear, $1/x^2$ weighting	
Standard calibration curve performance during accuracy and precision runs	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.18% to 2.75%
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 5.23%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 6 QCs	0.64 to 2.47%

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	Inter-batch %CV	≤ 6.45%
Selectivity & matrix effect	The detector responses are less than 20% of the BAY 1021189 response of the LLOQ (CS1) sample and less than 5% of the mean internal standards responses in 6 out of 6 tested matrices (includes hemolyzed and hyperlipidemic lots)	
Interference & specificity	No significant interference observed in all blanks and zero standards tested for potentially interfering concomitant medications and commonly used drugs tested.	
Hemolysis effect	One lot tested. Low and high QCs were prepared in this lot. IS normalized matrix factors were 0.997288 and 1.008296 for Low and High QCs, respectively.	
Lipemic effect	One lot tested. Low and high QCs were prepared in this lot. IS normalized matrix factors were 0.984621 and 1.006398 for Low and High QCs, respectively.	
Dilution linearity & hook effect	2000 µg/L tested (n=6) with a 20-fold dilution factor. Mean bias was -3.50%, CV 3.60%	
Bench-top/process stability	At least 25.25-hour bench-top stability for Low and High QC samples was established. Mean % bias was -2.25 and -5.11 for the low and high QCs, respectively. Precision (n=6) was 2.18 and 3.40% CV for the low and high QCs, respectively.	
Freeze-Thaw stability	Low and high QC samples were prepared, stored at -20°C and subjected to four freeze-thaw cycles. Mean % bias was determined to be 0.17 and 0.33 for the low and high QCs, respectively. Precision (CV, n=6) was 1.98 and 2.13% for the low and high QCs, respectively. Similar results were obtained for samples stored at -80°C.	
Long-term storage	Low and high QC samples were prepared and stored at -20°C and -80°C. Stability at -20°C was established for 651 days. Stability at -80°C was established for 665 days.	
Method ANI 10980		

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Materials used for standard calibration curve and concentration	Control human plasma and vericiguat (BAY 1021189) reference standard. Calibrator Concentrations: 1, 2, 20, 100, 200, 400, 800, and 1000 ng/mL	
Validation assay range	1 – 1000 ng/mL	
QCs	3, 5 and 750 ng/mL	
Regression model and weighting	Linear, $1/x^2$ weighting	
Standard calibration curve performance during accuracy and precision runs	Cumulative accuracy (%bias) from LLOQ to ULOQ	-6.43% to 5.4%
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 4.39%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 6 QCs	-0.31 to 3.73%
	Inter-batch %CV	≤ 5.21%
Selectivity & matrix effect	Mean internal standard normalized matrix factors for low and high QCs, each prepared in six lots of matrix (including 1 hyperlipemic and 1 hemolyzed) were 1.0165023 (low QC) and 1.0081658 (high QC)	
Interference & specificity	This method was a modification of ANI 10956, additional interference assessments were not conducted	
Hemolysis effect	One lot tested. Low and high QCs were prepared in this lot. IS normalized matrix factors were 1.019209 and 1.007229 for Low and High QCs, respectively.	
Lipemic effect	One lot tested. Low and high QCs were prepared in this lot. IS normalized matrix factors were 1.034192 and 1.0.987787 for Low and High QCs, respectively.	

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Dilution linearity & hook effect	2000 µg/L tested (n=6) with a 20-fold dilution factor. Mean bias was -3.92%, CV 4.02%	
Bench-top/process stability	At least 23.67-hour bench-top stability for Low and High QC samples was established. Mean % bias was -2.33 and -6.65 for the low and high QCs, respectively. Precision (n=6) was 1.08 and 1.02% CV for the low and high QCs, respectively.	
Freeze-Thaw stability	Low and high QC samples were prepared, stored at -20°C and subjected to four freeze-thaw cycles. Mean % bias was determined to be 4.44 and 7.64 for the low and high QCs, respectively. Precision (CV, n=6) was 5.99 and 1.23% for the low and high QCs, respectively. Similar results were obtained for samples stored at -80°C.	
Long-term storage	Low and high QC samples were prepared and stored at -20°C and -80°C. Stability at both temperatures was established for 734 days.	
Method MW1477		
Materials used for standard calibration curve and concentration	Control human plasma and vericiguat (BAY 1021189) reference standard. Calibrator Concentrations: 0.2, 0.5, 1, 2, 5, 10, 20, 50, 100, and 200 ng/mL	
Validation assay range	0.2 – 200 ng/mL	
QCs	0.6, 10, and 160 ng/mL	
Regression model and weighting	Linear, $1/x^2$ weighting	
Standard calibration curve performance during accuracy and precision runs	Cumulative accuracy (%bias) at LLOQ	-1.67%
	Cumulative precision (%CV) at LLOQ	4.39%

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Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 5 QCs	-1.02 to 3.23%
	Inter-batch %CV	≤ 2.52%
Selectivity & matrix effect	Mean internal standard normalized matrix factors for samples (n=5) prepared to contain vericiguat at concentrations of 1.00 and 100 µg/L were 0.977 and 1.027 for the 1.00 and 100 µg/L samples, respectively	
Interference & specificity	<5%. Assessed by comparing blank peak heights (n=6) to the mean peak height of a sample prepared at the LLOQ.	
Hemolysis effect	Not assessed	
Lipemic effect	Not assessed	
Dilution linearity & hook effect	1000 µg/L tested (n=6) with a 10-fold dilution factor. Mean bias was -2.37%, CV 2.41%	
Bench-top/process stability	At least 24 hour bench-top stability for Low, Medium and High QC samples was established. Mean % bias was < 10.5% for all concentrations. Precision (CV, n=6) was < 3.22% for all concentrations.	
Freeze-Thaw stability	Low and high QC samples were prepared, stored at < -15°C and subjected to three freeze-thaw cycles. Mean % bias was determined to be 3.10 and -0.919 for the low and high QCs, respectively. Precision (CV, n=6) was 2.86 and 1.44% for the low and high QCs, respectively.	
Long-term storage	Low, medium, and high QC samples were prepared and stored at < -15°C. Stability was established for at least 337 days for all concentrations.	

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4.2 PHARMACOMETRIC ASSESSMENT

4.2.1 The Applicant's Population PK analysis

Population PK (POP-PK) analyses were conducted by the Applicant to characterize the PK of vericiguat in subjects with HFrEF. The objectives of the Applicant's POP-PK analyses were to: 1) develop a POP-PK model that characterizes the vericiguat plasma concentration profile over time and describes the variability in vericiguat PK in subjects with HFrEF from the SOCRATES REDUCED and VICTORIA studies; 2) characterize the impact of intrinsic and extrinsic factors on vericiguat exposures; and 3) generate empirical Bayes estimates of vericiguat exposures (for example, individual AUC0-24 and Cmax) to support exposure-response (E-R) analyses for clinical efficacy and safety. Previously, a preliminary POP-PK model (Study # 17401, Report # 05GJCP) was developed using data from SOCRATES-REDUCED. During the development, the preliminary POP-PK model was used to determine vericiguat exposures for evaluation of the exposure-response relationship for SBP and NT-proBNP in subjects with HFrEF from SOCRATES-REDUCED.

The Applicant's integrated POP-PK analyses included data from SOCRATES-REDUCED (Phase 2b) and VICTORIA (Phase 3) studies conducted in subjects with HFrEF. VICTORIA was a randomized, placebo-controlled, parallel-group, double-blind Phase 3 study where subjects were randomized 1:1 to receive vericiguat or placebo on a background of standard of care. SOCRATES-REDUCED was a randomized parallel-group, placebo-controlled, double-blind Phase 2 study. Both studies included men and women aged 18 years or older with chronic HF (NYHA Class II-IV), reduced ejection fraction (< 45%), elevated natriuretic peptides, and previous HF decompensation (defined as HF hospitalization or use of intravenous diuretics for HF [without hospitalization]).

Dose levels ranged from starting doses of 1.25 mg (lowest dose in SOCRATES-REDUCED) to a target dose of 10 mg administered once daily in multiple-dose regimens. SOCRATES-REDUCED included 5 dosing arms – placebo, 1.25 mg fixed dose, 2.5 mg fixed dose, and 2 titrated arms each with a 2.5 mg starting dose with dose doublings approximately every 2 weeks to reach a targeted therapeutic dose of 5 or 10 mg. In the VICTORIA study, subjects followed a SBP-guided titration scheme with a starting dose of 2.5 mg and dose doubling every 2 weeks up to a target dose of 10 mg as tolerated. In both studies, doses could be reduced or interrupted at any point during the study based on the SBP-guided titration scheme. A brief description of the study design, dosing regimen, population etc. are provided in Section 3.3.1.

In the SOCRATES-REDUCED study, sparse PK samples were collected at pre-1st dose and 1 to 3 hours, 4 to 6 hours, and 20 to 24 hours post-dose before intake of the next dose of study drug on multiple visits. For the VICTORIA study, a single PK sample at Day 1 (pre-dose), Visit Week 16, Visit Week 48, yearly, and final visit (~4 samples per subject) was collected. Collected samples were analyzed using a HPLC with tandem mass spectrometry method for the determination of vericiguat in human plasma (Section 4.1). The final dataset for the POP-PK

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analyses consists of a total of 8092 quantifiable vericiguat PK samples from a total of 2321 subjects. Missing observations (concentrations below the limit of quantification) were excluded from the analysis.

The PPO-PK data was modeled using non-linear mixed effects in NONMEM. The methodology included - 1) exploratory data analysis; 2) base structural model development; 3) evaluation of covariate effects; 4) model refinement; and 5) model evaluation. The steady-state vericiguat exposures were simulated in subjects with HFrEF included in the analysis dataset using individual Bayesian parameter estimates from the final model and a fixed dosing regimen of 10 mg to study the magnitude of intrinsic factor effects on vericiguat exposures.

The structural model developed by the Applicant consisted of a one-compartmental PK model with absorption characterized by a first order absorption rate constant, distribution characterized by apparent volumes of compartment, and elimination characterized by a first order elimination rate constant. An exponential variance model was used to describe interindividual variability (IIV) in first-order absorption rate constant (ka), apparent clearance (CL/F), and apparent central volume of distribution (Vc/F) and a combined additive and proportional variance model was used to describe residual variability (RV). Since apparent PK parameters were estimated, a covariance between CL/F and Vc/F was included in the model to account for IIV in bioavailability (F1). Bioavailability was fixed to 1 and a covariate effect of dose levels on F1 was included in the model. Subjects from the 5.0-mg dose group had a bioavailability of approximately 84% of those from the 2.5-mg dose group. Furthermore, the subjects from the 10-mg dose group had a bioavailability of approximately 73% of those from the 2.5-mg dose group.

Covariates evaluated in the Applicant's POP-PK model are described in **Table 9**. Stepwise covariate analysis was performed using forward selection and backward elimination processes. All covariates were assumed to have remained constant throughout the study period and values collected at the baseline visit were used, except for body weight, bilirubin, albumin, and estimated glomerular filtration rate (eGFR), where baseline and time-varying values were included in the dataset.

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Table 9 Covariates Included in the Applicant's POP-PK analysis.

Covariates	Reason for Investigation	Parameter
Body Weight	Evaluate impact of body weight on each of the PK parameters	CL/F, V/F, and k_a
Bilirubin	Impact of bilirubin differences on metabolism	CL/F
eGFR (MDRD)	Impact of renal function on CL	CL/F
Albumin	Extensively protein bound	CL/F, V/F, and k_a
Sex	Evaluate difference in PK by sex	CL/F, V/F
Race	Evaluate difference in PK by race; previous studies had limited distribution of subjects for race categories	CL/F, V/F
Ethnicity	Evaluate difference in PK by ethnicity	CL/F, V/F
Age	Evaluate difference in PK by age	CL/F, V/F
Baseline Left Ventricle Ejection Fraction	Indicative of disease state	CL/F, V/F
Baseline New York Heart Association Functional Classification Group	Indicative of disease state	CL/F, V/F
Baseline NT-proBNP	Indicative of disease state	CL/F, V/F
Atrial Fibrillation	Affecting NT-proBNP; to be used in conjunction with NT-proBNP	CL/F
Concomitant Medications[a]	Acid-reducing agents have been shown to reduce exposure	k_a, F
Dose	Check for dose-dependent PK	F, k_a

Abbreviations: CL, clearance; CL/F, apparent clearance; eGFR, estimated glomerular filtration rate; F, bioavailability fraction; ka, first-order absorption rate constant; MDRD, modification of diet in renal disease; NT-proBNP, N-terminal pro b-type natriuretic peptide; PK, pharmacokinetic; V/F, apparent volume of distribution.
[a] Concomitant medication were examined provided there was adequate representation of that concomitant medication within the dataset (for example, ~ 10%), and there was appropriate dosing information collected. Note: Bilirubin, creatinine clearance, albumin, sex, race, and age were all included in the subject population pharmacokinetic model from SOCRATES-REDUCED.

Source: The Applicant's POP-PK Report # 05D7T5 (Table 3).

The Applicant's analysis indicates that dose was a significant predictor of F1 (100%, 84%, and 73% relative F1 for ≤ 2.5, 5, and ≥ 10 mg dose groups, respectively). Baseline and time-varying body weight were significant predictors of CL/F and Vc/F, respectively. In addition, age, bilirubin, estimated glomerular filtration rate, sex, albumin, use of proton pump inhibitor, use of any drugs affecting gastric pH, and NT-proBNP were not found to be significant predictors of vericiguat exposures.

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Table 10 Parameter Estimates of the Final POP-PK Model

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability[a]	
	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				

Abbreviations: CCV, constant coefficient of variation; %CV, coefficient of variation expressed as a percent; F, drug concentration in the central compartment; IIV, interindividual variability; NA, not applicable; NE, not estimated; %RSE, relative standard error expressed as a percent; RV, residual variability.

Parameter-covariate relationships were described as:

$$CL/F = 1.09 \times \left(\frac{WEIGHTBL}{77.6}\right)^{0.632}$$

$$V_c/F = 46.8 \times \left(\frac{WEIGHT}{77.6}\right)^{0.654}$$

$$k_a = 1.62$$

$$F1 = 1.00 \times e^{-0.178 \times DOSE2} \times e^{-0.320 \times DOSE3}$$

[a] Eta shrinkage: eta_CL/F: 14.4%, eta_V_c/F: 58.1%, eta_k_a: 85.4%.

[b] The calculated correlation coefficient (r) associated with cov(IIV in V_c/F, IIV in CL/F) was 0.183 with $r^2 = 0.0333$.

[c] The residual variability (%CV) was calculated using the following equation: $(SQRT(F^2 \times 0.117+21.3)/F) \times 100$.

Source: The Applicant's POP-PK Report # 05D7T5 (Table 13).

The parameter estimates of the final POP-PK model including fixed and random effects parameters and their associated precisions (%RSE, relative standard error expressed as a percent) for the final vericiguat model are presented in the table above.

The qualification of the final POP-PK model was performed using the goodness of fit plots. Goodness-of-Fit plots for the final POP-PK model for vericiguat plasma concentrations are presented in the figure below.

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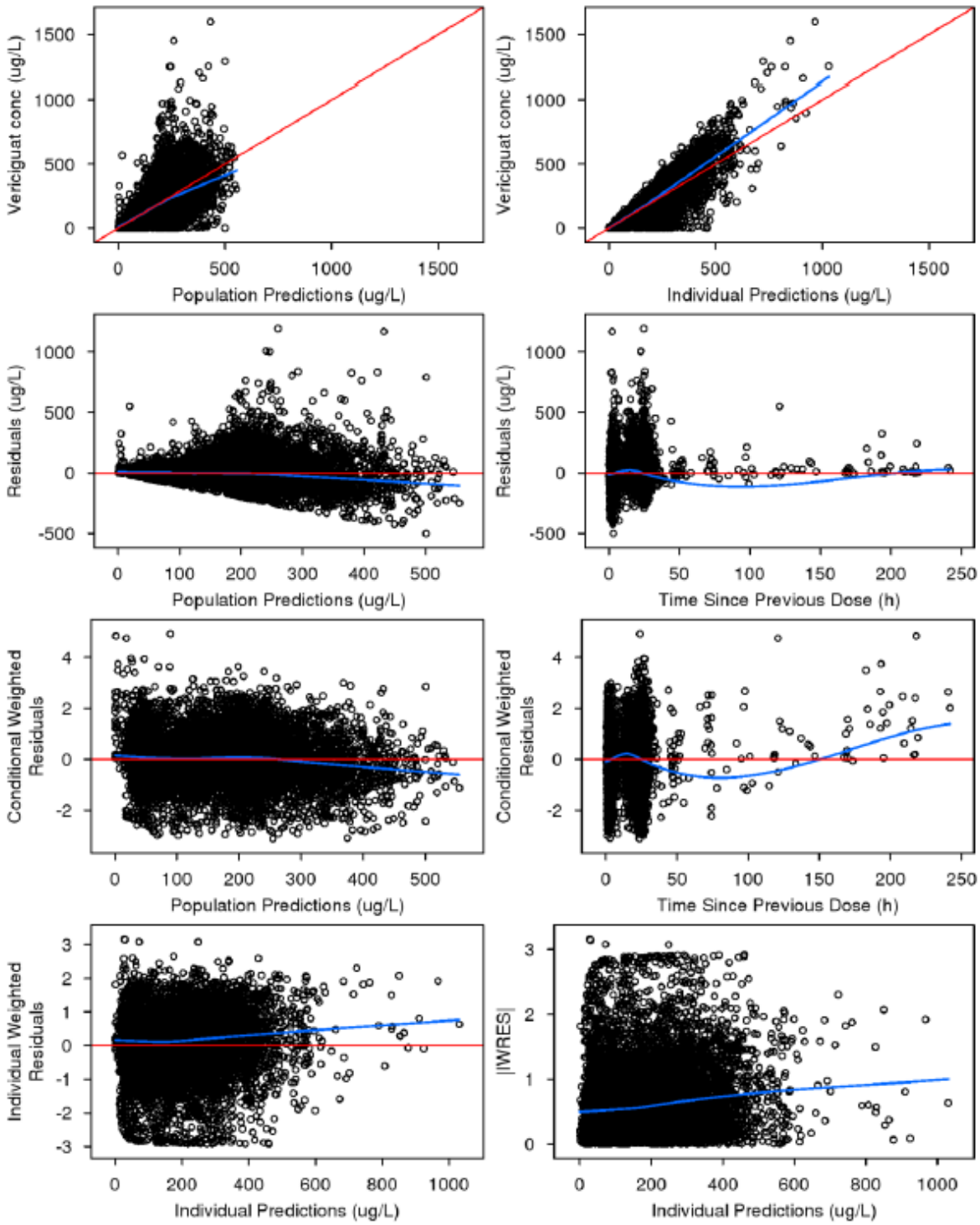
Figure 6 Goodness-of-Fit Plots for the Final POP-PK Model



Source: The Applicant's POP-PK Report # 05D7T5 (Figure 7).

Furthermore, a prediction-corrected visual predictive check (VPC) was used to evaluate the predictive performance of the vericiguat model. The prediction from simulation of 1000 replicates with the same design (and overall population; as well as stratified by dose groups)

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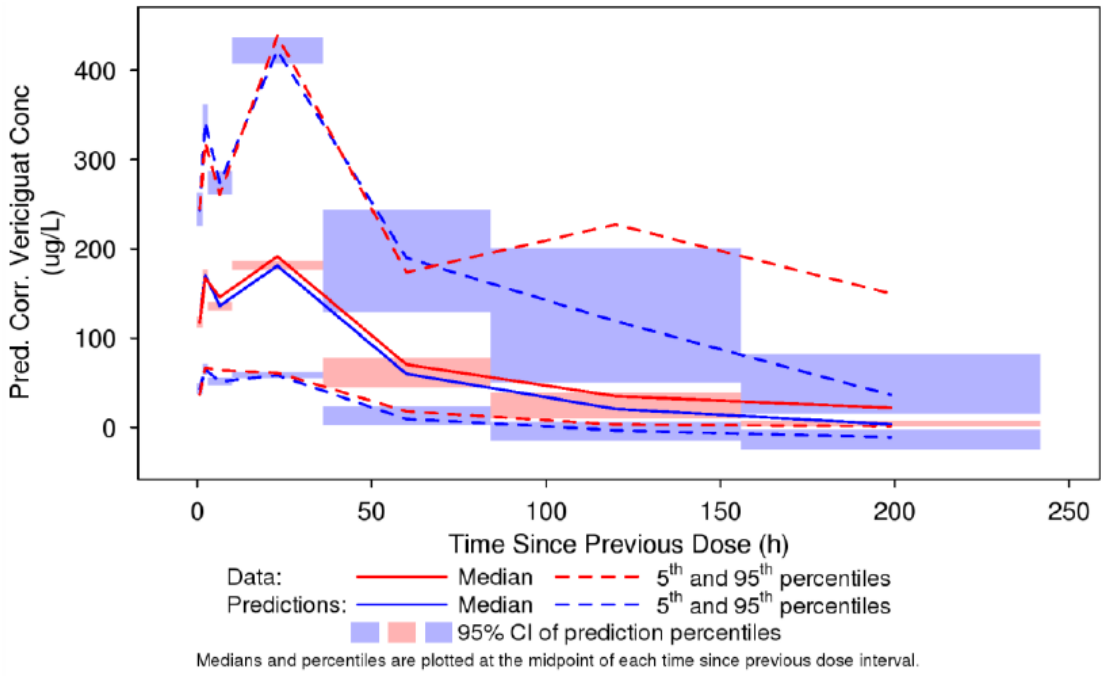
using the estimates of the population means and variability from the final POP-PK model were overlaid with the observed data with the median values along with the 5th and 95th percentiles (with associated CIs) from the simulated concentration-time profiles. Visual predictive check for the final population pharmacokinetic model for vericiguat plasma concentrations is presented in the figure below.

Figure 7 Visual Predictive Check of the Final POP-PK Model



Abbreviation: CI, confidence interval; conc, concentration; pcVPC, prediction-corrected visual predictive check; Pred Corr, prediction corrected.

Source: The Applicant's POP-PK Report # 05D7T5 (Figure 6).

The Applicant simulated the steady-state vericiguat exposures in subjects with HFrEF (included in the analysis dataset) using individual Bayesian parameter estimates from the final model and a fixed dosing regimen of 10 mg to study the magnitude of intrinsic factor effects on vericiguat exposures. Furthermore, individual exposures (AUC0-24, Cmax, and trough concentration) were simulated using each individual's empirical Bayesian estimates from the final model and dosing history.

Consistent with the fact that body weight was a statistically significant covariate on CL/F with a positive exponent, the steady-state AUC0-24 was 27% higher in the < 60 kg body weight group and 19.6% lower in the > 90 kg body weight group, compared to the reference group (60 to 90 kg body weight group). Similarly, the steady-state Cmax was 27% higher in the < 60 kg body weight group and 19.4% lower in the > 90 kg body weight group, compared to the reference group (60 to 90 kg body weight group).

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Summary of the estimated steady-state vericiguat plasma exposures for the HFrEF population from the VICTORIA study using the final POP-PK model is described in table below.

Table 11 Summary of Estimated Parameters at Steady-State (by dose level)

Exposure Measure	Statistic	Dose Level 2.5 mg	5 mg	10 mg	Overall
C_{max} (ng/mL)	Mean (SD)	126 (32.9)	215 (62.6)	368 (109)	332 (126)
	Median	120	200	349	326
	Geo Mean (Geo %CV)	122 (26.0)	207 (28.3)	354 (28.8)	306 (43.8)
	%CV	26.2	29.1	29.5	38.0
	Min, Max	66.3, 247	91.4, 499	134, 1050	66.3, 1050
	5th, 95th	80.6, 183	135, 327	223, 561	130, 546
	25th, 75th	102, 147	172, 255	292, 427	252, 406
	n	139	240	1546	1925
C_{trough} (ng/mL)	Mean (SD)	78.2 (28.9)	136 (53.4)	231 (95.8)	208 (100)
	Median	71.9	124	215	192
	Geo Mean (Geo %CV)	73.3 (37.5)	126 (39.7)	213 (42.3)	185 (54.1)
	%CV	37.0	39.3	41.4	48.2
	Min, Max	17.7, 192	42.7, 384	24.4, 866	17.7, 866
	5th, 95th	41.8, 131	68.4, 232	109, 399	71.5, 390
	25th, 75th	58.4, 96.8	99.9, 163	164, 282	136, 264
	n	139	240	1546	1925
Half-Life (h)	Mean (SD)	31.2 (8.55)	31.9 (8.36)	31.9 (10.5)	31.9 (10.1)
	Median	29.5	30.4	30.2	30.2
	Geo Mean (Geo %CV)	30.2 (26.5)	30.9 (26.4)	30.5 (30.6)	30.5 (29.8)
	%CV	27.4	26.2	32.9	31.8
	Min, Max	9.84, 71.6	13.0, 67.5	6.41, 138	6.41, 138
	5th, 95th	20.2, 48.3	19.8, 46.1	18.8, 48.4	19.3, 48.3
	25th, 75th	26.4, 34.5	26.9, 37.5	25.2, 37.0	25.4, 36.9
	n	139	240	1546	1925
AUC_{0-24} (ng × h/mL)	Mean (SD)	2440 (745)	4220 (1400)	7190 (2460)	6480 (2720)
	Median	2330	3900	6760	6200
	Geo Mean (Geo %CV)	2340 (30.2)	4010 (32.6)	6810 (33.8)	5900 (47.4)
	%CV	30.5	33.2	34.3	42.0
	Min, Max	1060, 5300	1670, 10600	2180, 23100	1060, 23100
	5th, 95th	1450, 3810	2460, 6820	4000, 11600	2470, 11300
	25th, 75th	1930, 2970	3260, 5010	5450, 8540	4650, 8040
	n	139	240	1546	1925
Apparent Clearance (L/h)	Mean (SD)	1.12 (0.332)	1.10 (0.350)	1.13 (0.379)	1.12 (0.373)
	Median	1.07	1.07	1.07	1.07
	Geo Mean (Geo %CV)	1.07 (30.2)	1.04 (32.6)	1.07 (33.8)	1.06 (33.4)
	%CV	29.8	31.9	33.7	33.2
	Min, Max	0.472, 2.35	0.393, 2.51	0.315, 3.33	0.315, 3.33
	5th, 95th	0.655, 1.72	0.614, 1.70	0.627, 1.82	0.627, 1.80
	25th, 75th	0.843, 1.29	0.835, 1.28	0.851, 1.33	0.847, 1.32
	n	139	240	1546	1925

Source: The Applicant's POP-PK Report # 05D7T5 (Table 14).

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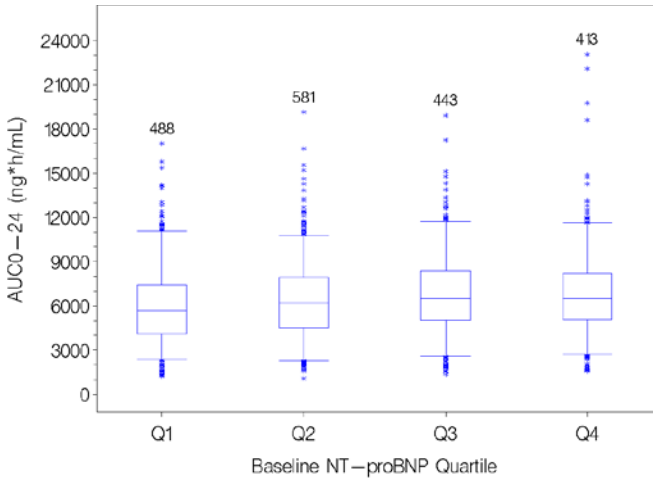
Comparison of vericiguat steady-state area under the plasma concentration-time curve in subjects with HFrEF from the VICTORIA is provided below.

Figure 8 AUCs at Steady-State by Baseline NT-proBNP Quartiles

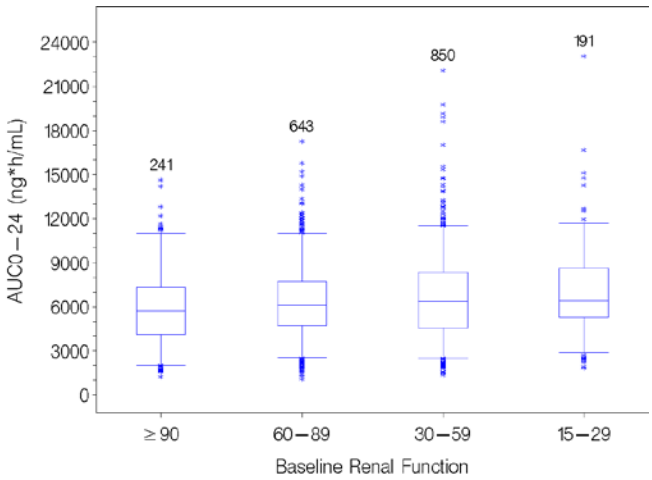


Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Asterisks show data points outside this range. The number of subjects is above each box.

Abbreviation: AUC0-24, area under the plasma concentration-time curve from time 0 to 24 hours; HFrEF, heart failure with reduced ejection fraction. Note: The dose for each subject was derived as the most frequent dose between Days 57 and 168.

Source: The Applicant's POP-PK Report # 05D7T5 (Figure 15).

Figure 9 AUCs at Steady-State by Baseline Renal Function



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Asterisks show data points outside this range. The number of subjects is above each box.

Abbreviation: AUC0-24, area under the plasma concentration-time curve from time 0 to 24 hours; HFrEF, heart failure with reduced ejection fraction. Note: The dose for each subject was derived as the most frequent dose between Days 57 and 168.

Source: The Applicant's POP-PK Report # 05D7T5 (Figure 15).

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Reviewer's comments:

The Applicant's model of vericiguat PK is acceptable to be used for PK labeling description, identifying covariates of vericiguat exposure, and deriving PK concentrations for the exposure-response analyses

The Applicant modeled the PK data of vericiguat from Phase 2 and Phase 3 studies listed in Table 1, which included sparse sampling designs in subjects with HFrEF. During the model development, high-influence data points (114 records from 110 subjects) were identified as concentrations measured > 250 hours after the last dose (approximately 8 to 10 half-lives for vericiguat) and excluded from the analysis during the base model development. A limit of 250 hours was identified considering linear PK of vericiguat that would eliminate a majority of the drug from the body after a duration of 8 to 10 half-lives. There were 8092 concentrations from 2321 subjects included for the development of the vericiguat POP-PK model. This approach seems reasonable, especially because the effect of high-influence data on the PK parameters was assessed in the final model. Inclusion of the high-influence data points (time since last dose > 250 hours) in the final model estimation resulted in more than a 10% change in fixed effect (0.32% to 17.0% change) and random effect parameters (4.35% to 2610% change), compared to the model without high-influence data points.

The Applicant's 1-compartment model with first-order absorption, linear elimination, and moderate between-subject variability reasonably described the plasma concentration-time profile for vericiguat in subjects with HFrEF. Disease related factors examined in the POP-PK analysis that did not influence vericiguat exposure in subjects with HFrEF included baseline measures of NT-proBNP, left ventricular ejection fraction, New York Heart Association class, albumin, bilirubin, or eGFR. Differences in exposure observed in the disease related factor baseline NT-proBNP or other intrinsic factor categories examined are driven by underlying differences in body weight. The final model parameter estimates and associated uncertainty in the estimation reported in Table 3 are acceptable to derive vericiguat exposures for the exposure-response analysis.

It is reasonable to use the final vericiguat model for simulating the concentration-time profiles in order to determine drug exposure at clinical doses.

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4.2.2 The Applicant's Exposure-Response Analysis

Exposure-Response (E-R) analyses were conducted by the Applicant to quantify the relationship between vericiguat plasma exposures and efficacy or safety in subjects with HFrEF. The objectives of the E-R analyses were to explore and quantify the relationship between vericiguat plasma exposures and efficacy (time to cardiovascular outcomes) and safety (symptomatic hypotension, syncope, and change from baseline in systolic blood pressure measurements) in the Phase 3 study (VICTORIA). VICTORIA was a randomized, placebo-controlled, parallel-group, double-blind Phase 3 study (see Section 3.3.1).

During the development, the Applicant developed POP-PK model to characterize the pharmacokinetics of vericiguat in subjects with HFrEF (See Section 4.2.1). Vericiguat exposures (AUC0-24h and Cmax; see below) generated using the final POP-PK model were used in the assessment of exposure-response relationship. For this purpose, the Applicant utilized final POP-PK model, individual empirical Bayesian PK parameter estimates, and individual's dosing history from VICTORIA.

In VICTORIA, efficacy outcome data (i.e., the time to the composite endpoint of CV death or first HF hospitalization) were collected throughout the study. Similarly, continuous SBP measurements were collected at baseline; 2 h post-dose on Day 1; during Day 14 and Day 28 visits, as well as Weeks 16, 32, 48, 64, 80, 96, 112, and 128; final visit; and discontinuation. The E-R analyses included on-treatment population in VICTORIAA. A total of 1959 subjects treated with vericiguat (who had at least one evaluable PK measurement; approximately 78% of total subjects randomized to vericiguat) were included in the E-R safety and efficacy analyses. Due to the flexible (titration-based) dosing regimen in VICTORIA, the Applicant highlighted that most events during the titration phase were associated with lower exposure and after the titration phase, exposure was confounded by a small portion of subjects' inability to reach and remain on a stable 10-mg dose. For this purpose, the Applicant utilized various exposure metrics.

In the primary E-R efficacy analysis, following vericiguat exposure metrics were used to assess the impact of exposure on time to the composite endpoint of CV death or first HF hospitalization:

- Steady-state AUC0-24[†]
- Time-weighted average AUC0-24[‡]
- Daily AUC0-24

[†]AUC based on the most frequent dose for a subject from Days 57 to 168; [‡]AUC from the first dose date until the date of the CV event for subjects who had the event or until the date of censor for subjects who did not experience a CV event.

In the exploratory E-R safety analysis, following vericiguat exposure metrics were used to assess the impact of exposure on the safety endpoint (longitudinal measures of SBP):

- AUC0-24
- Cmax

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The E-R data was modeled using a simulation-based, visual predictive check methodology to assess concordance between the model-based simulated data and the observed data. Survival analysis using an E-R Cox proportional hazards model was used to describe the relationship between efficacy endpoint, time to first occurrence of HF hospitalization or CV death, and vericiguat exposure and covariates. Exposure-response modeling of time-to-event (TTE) endpoints using Cox proportional hazards modeling was performed using R (Ver 3.4.3) software.

The methodology included – 1) generation of individual estimates of exposure based on the POP-PK model, 2) exploratory data analysis, 3) base structural model development incorporating drug exposure, 4) evaluation of covariate effects, 5) model refinement, and 6) model evaluation. Prior to modeling, the Applicant conducted exploratory analysis to 1) understand the confounding effects of the flexible dose titration regimen on the dose/E-R relationships observed in the VICTORIA study and 2) define whether a more extensive quantitative assessment of the relationship between E-R for efficacy is needed. The Applicant included following covariates: baseline age, sex, geographic region, index event, eGFR at randomization, baseline NYHA class, use of sacubitril/valsartan at baseline, NT-proBNP, baseline ejection fraction, and race. To gain further insight into the E-R relationship, the Applicant also generated Kaplan-Meier (KM) plots for exposure quartiles of the subset of subjects who were able to titrate to the 10-mg dose and remained on the 10-mg dose from Day 56 until end of trial or date of CV event without any dose interruption or dose reduction.

Performance of the TTE models were evaluated by a visual predictive check which was the KM curve of the observed data plus a 95% prediction interval of simulated data from the TTE model with 500 replicates. To generate the VPC, the selected final model was used to simulate 500 sets of event times. Subsequently, KM survival curves with 95% confidence intervals (CIs) were plotted for the observed events and for the 2.5, 50, and 97.5 percentiles. Finally, KM plots were also stratified by quantiles of vericiguat exposure/covariates to assess if exposure/covariate dependencies are adequately characterized. The parameter estimates and standard errors are presented for the final E-R efficacy model. Similarly, confidence intervals of the hazard ratios for each parameter are reported. In VICTORIA, a flexible (titration-based) dosing regimen was utilized and the most stable steady-state dose was 10 mg for ~80% of the subjects, 5 mg and 2.5 mg for ~13% and ~7% of subjects, respectively.

Table 12 Summary Statistics of the Occurrence of Cardiovascular Events (by Treatment)

Endpoint		Treatment		Overall
		Placebo	Vericiguat	
Cardiovascular Event, n (%)	No	1714 (68.2)	1438 (73.4)	3152 (70.5)
	Yes	801 (31.8)	521 (26.6)	1322 (29.5)

n, number of subjects.

Source: The Applicant's E-R Report # 05D7SZ (Table 8).

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The summary statistics of occurrence of cardiovascular events indicates that ~29.5% of subjects had a CV event of death or HF hospitalization and ~70.5% were censored (no CV event or were lost to follow-up). The median days to the CV event in that groups were 143 days (1 to 899 days). Subjects receiving vericiguat experienced fewer CV events (~26.6%) compared to those receiving placebo (~31.8%). In addition, the mean days from the first dose to CV event for the subjects receiving vericiguat (230 days) was longer compared to those receiving placebo (178 days).

The Applicant's E-R efficacy analysis included the on-treatment population in the VICTORIA study (with evaluable PK; 78% of total subjects randomized to vericiguat and placebo) and is a different population set compared to that of the primary statistical analysis for efficacy. After exclusions (11 subjects with no PK available, 390 subjects with no evaluable PK, and 159 subjects from China, PK pending), a total of 4474 subjects remained in the E-R efficacy analysis dataset. All subjects on placebo (set to zero) were included in the E-R analyses. Summary statistics of vericiguat time-weighted average exposure measures (AUC0-24 and Cmax) are presented in **Table 13**. The Applicant's data indicated that the steady-state AUC0-24 did not affect significantly due to transient dose reduction or interruption.

Table 13 Summary Statistics of Vericiguat Time-Weighted Average Exposure Measures for the Exposure-Response Efficacy Analysis (by Dose).

		Mode of Dose (mg)			
Exposure Measure	**Statistic**	**2.5**	**5**	**10**	**Overall**
Time-Weighted Average Vericiguat $AUC_{0\text{-}24}$ (ng × h/mL)	Mean (SD)	2395.2808 (1156.1650)	4048.2619 (1478.2943)	6431.7237 (2333.7731)	5788.4445 (2561.9580)
	Median	2220.0000	3870.0000	6020.0000	5530.0000
	Min, Max	40.800, 7500.000	411.000, 8100.000	1920.000, 22400.000	40.800, 22400.000
	n	213	168	1578	1959
Time-Weighted Average Vericiguat C_{max} (ng/mL)	Mean (SD)	123.1700 (55.8428)	206.1583 (69.2694)	329.2909 (104.0847)	296.3200 (119.6140)
	Median	116.0000	195.5000	315.0000	290.0000
	Min, Max	2.110, 359.000	21.200, 398.000	103.000, 1020.000	2.110, 1020.000
	n	213	168	1578	1959
Clearance (L/h)	Mean (SD)	1.1172 (0.3345)	1.0731 (0.3604)	1.1251 (0.3769)	1.1198 (0.3713)
	Median	1.0700	1.0300	1.0800	1.0700
	Min, Max	0.472, 2.350	0.485, 2.550	0.315, 3.330	0.315, 3.330
	n	213	168	1578	1959

AUC0-24, area under the plasma concentration-time curve from time 0 to 24 hours; Cmax, maximum concentration; Max, maximum; Min, minimum; n, number of subjects; SD, standard deviation. Note: [or] indicates respective endpoint is included in the interval and (or) indicates respective endpoint is not included in the interval. Mode of dose is the most frequent dose within the window of time used for exposure calculations.

Source: The Applicant's E-R Report # 05D7SZ (Table 5).

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Summary statistics of vericiguat measures (AUC0-24 and Cmax) are presented in **Table 14**.

Table 14 Summary Statistics of Vericiguat Time-Weighted Average Exposure Measures for the Exposure-Response Efficacy Analysis (Top: by Quartiles of Time-Weighted Average AUC0-24 and Bottom: by Quartiles of Steady-State AUC0-24)

Exposure Measure	Statistic	Quartiles of Time-Weighted Average AUC_{0-24}				Overall
		[40.8, 4125)	[4125, 5530)	[5530, 7290)	[7290, 22400]	
Time-Weighted Average Vericiguat AUC_{0-24} (ng × h/mL)	Mean (SD)	2849.70 (921.49)	4838.23 (406.47)	6294.02 (489.34)	9152.18 (1962.60)	5788.44 (2561.96)
	Median	3005.00	4870.00	6260.00	8570.00	5530.00
	Min, Max	40.8, 4120.0	4130.0, 5520.0	5530.0, 7280.0	7290.0, 22400.0	40.8, 22400.0
	n	490	485	493	491	1959
Time-Weighted Average Vericiguat C_{max} (ng/mL)	Mean (SD)	154.54 (52.26)	256.78 (22.75)	323.94 (25.28)	449.13 (86.48)	296.32 (119.61)
	Median	161.50	257.00	324.00	426.00	290.00
	Min, Max	2.1, 274.0	204.0, 322.0	267.0, 446.0	352.0, 1020.0	2.1, 1020.0
	n	490	485	493	491	1959

Exposure Measure	Statistic	Quartiles of Steady-State AUC_{0-24}				Overall
		[1060,4650)	[4650,6200)	[6200,8040)	[8040,23100]	
Steady-State Vericiguat AUC_{0-24} (ng × h/mL)	Mean (SD)	3349.00 (883.68)	5444.21 (446.14)	7023.84 (527.35)	10065.59 (2032.62)	6478.09 (2717.67)
	Median	3560.00	5420.00	6970.00	9430.00	6200.00
	Min, Max	1060.0, 4640.0	4650.0, 6190.0	6200.0, 8030.0	8040.0, 23100.0	1060.0, 23100.0
	n	481	480	479	485	1925
Steady-State Vericiguat C_{max} (ng/mL)	Mean (SD)	182.07 (50.96)	288.84 (25.14)	360.81 (26.83)	493.35 (89.99)	331.60 (126.00)
	Median	188.00	289.50	360.00	466.00	326.00
	Min, Max	66.3, 284.0	223.0, 360.0	295.0, 476.0	382.0, 1050.0	66.3, 1050.0
	n	481	480	479	485	1925

AUC0-24, area under the plasma concentration-time curve from time 0 to 24 hours; Cmax, maximum concentration; Max, maximum; Min, minimum; n, number of subjects; SD, standard deviation. Note: [or] indicates respective endpoint is included in the interval and (or) indicates respective endpoint is not included in the interval. The dose for each subject was derived as the most frequent dose between Days 57 and 168.

Source: The Applicant's E-R Report # 05D7SZ (Table 6 and 7).

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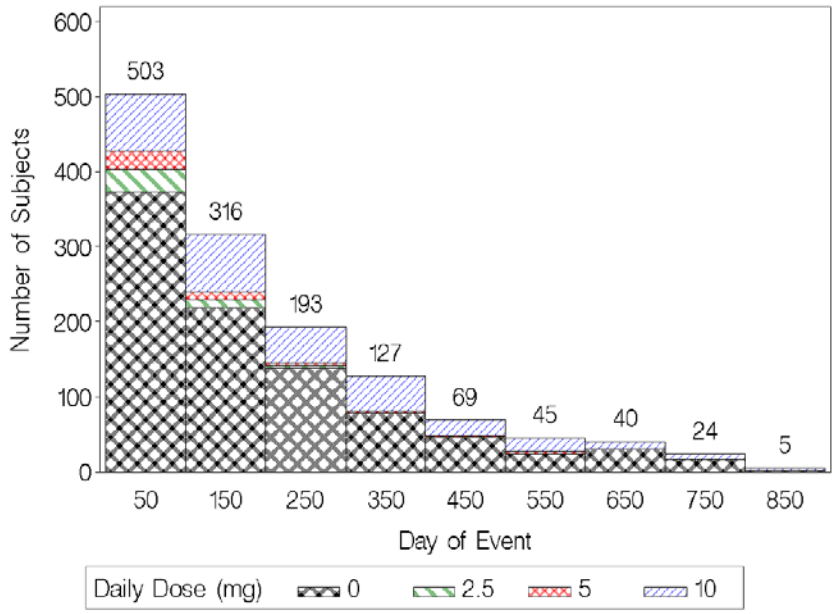
Table 15 Summary Statistics of Vericiguat Time-Weighted Average Exposure Measures for the Exposure-Response Efficacy Analysis (by CV Events)

Exposure Measure	Statistic	Cardiovascular Event		Overall
		No	Yes	
Time-Weighted Average Vericiguat $AUC_{0\text{-}24}$ (ng × h/mL)	Mean (SD)	6008.3727 (2537.5402)	5181.4257 (2533.2620)	5788.4445 (2561.9580)
	Median	5745.0000	4930.0000	5530.0000
	Min, Max	311.000, 21000.000	40.800, 22400.000	40.800, 22400.000
	n	1438	521	1959
Time-Weighted Average Vericiguat C_{max} (ng/mL)	Mean (SD)	307.6697 (117.5403)	264.9939 (119.8105)	296.3200 (119.6140)
	Median	298.5000	261.0000	290.0000
	Min, Max	16.400, 960.000	2.110, 1020.000	2.110, 1020.000
	n	1438	521	1959
Clearance (L/h)	Mean (SD)	1.1236 (0.3795)	1.1094 (0.3475)	1.1198 (0.3713)
	Median	1.0800	1.0700	1.0700
	Min, Max	0.329, 3.170	0.315, 3.330	0.315, 3.330
	n	1438	521	1959

AUC0-24, area under the plasma concentration-time curve from time 0 to 24 hours; Cmax, maximum concentration; Max, maximum; Min, minimum; n, number of subjects; SD, standard deviation.

Source: The Applicant's E-R Report # 05D7SZ (Table 10).

Figure 10 Frequency Distribution of Days to Cardiovascular Event (by Dose).



The number under each bar represents the median of the range of values for that bar. The number above each bar represents the number of subjects in each bar.

Source: The Applicant's E-R Report # 05D7SZ (Figure 2).

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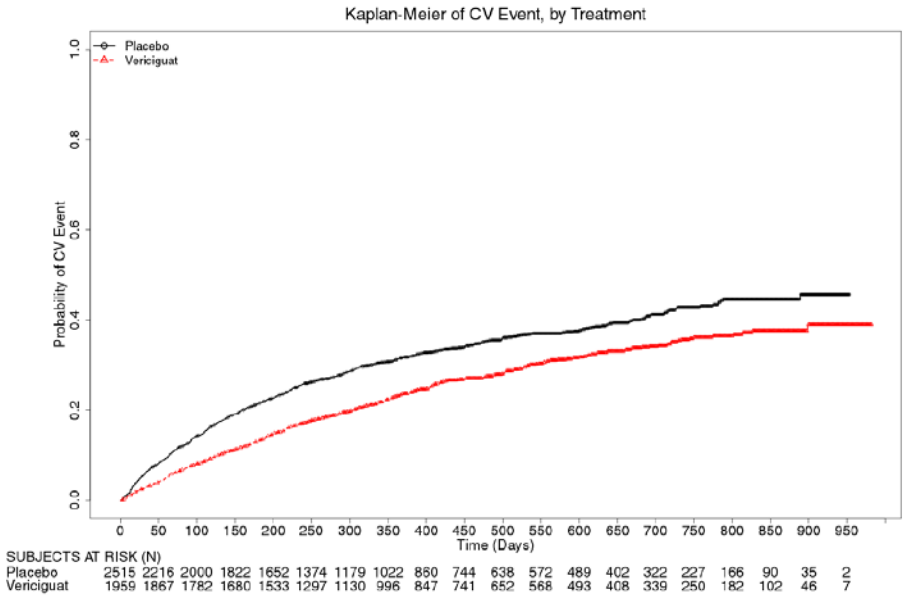
The frequency distribution of days to the CV event for subjects (with the event stratified by dose) is presented in **Figure 10**. Approximately 62% of the CV events occurred within the first 200 days of treatment.

The Applicant's KM curves for the probability of CV event by treatment is presented below.

Figure 11 Kaplan-Meier Plot of Probability of Cardiovascular Event Versus Time (Overall).



Source: The Applicant's E-R Report # 05D7SZ (Figure 3).

Figure 11 indicates that the vericiguat treatment arm had a fewer CV events (across study duration) compared to placebo. In general, higher vericiguat exposures were associated with a lower probability of CV events. The KM curves of the probability of CV event by quartiles of vericiguat exposure are presented below (**Figure 12**; quartiles of time-weighted average AUC0-24 and quartiles of time-weighted average Cmax). The Applicant's analysis indicated a higher vericiguat exposures were associated with a lower probability of CV event. The Applicant highlighted that the higher CV event rates in the 2 lower exposure quartiles are possibly associated with the dose titration, dose reduction, and dose interruption in subjects on vericiguat. Considering a flexible titration-based dosing regimen, these exposure metrics were likely to be affected by transient dose reduction or interruption. The PK plots were also constructed using other exposures metrics (steady-state AUC0-24) which indicated that efficacy is comparable across quartiles of individual steady-state AUC0-24, as well as quartiles of individual CL/F (**Figure 13**). Thus, both vericiguat exposure measures were statistically significant ($P < 0.05$) predictors of the probability of CV outcomes. The summary of the evaluation of vericiguat exposure measures on the time to CV outcomes is provided below (**Table 16**).

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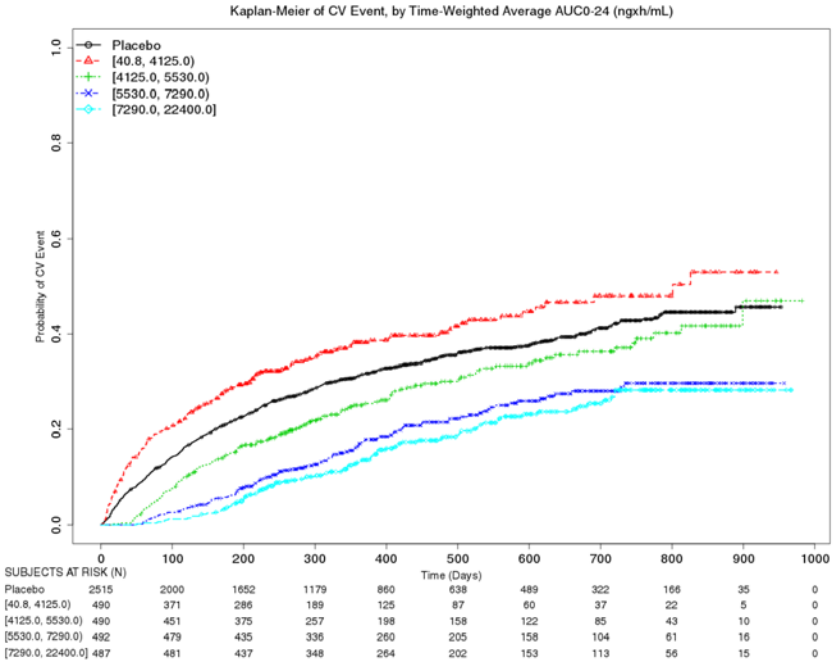
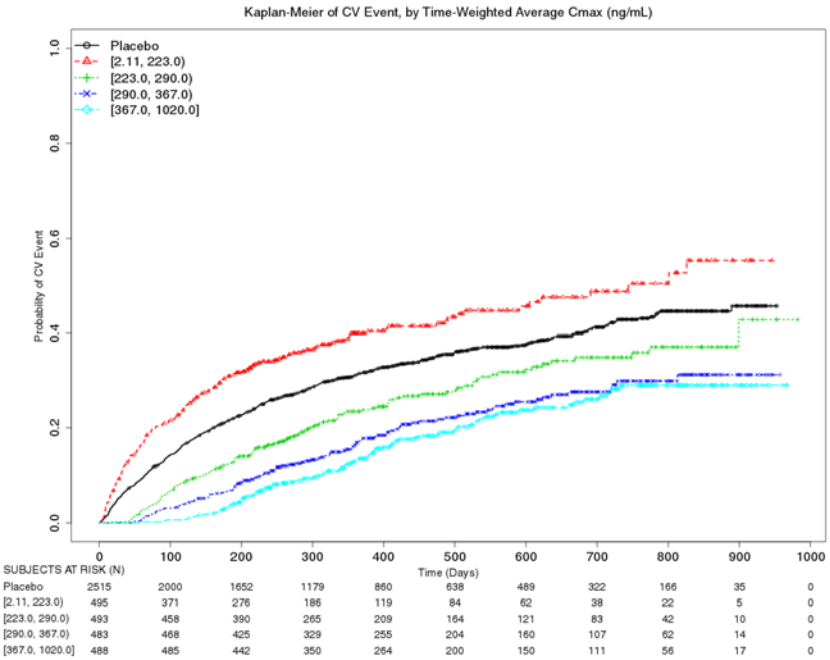
Figure 12 Kaplan-Meier Plot of Probability of Cardiovascular Event Versus Time (top: Quartiles of Time-Weighted Average AUC and bottom: Quartiles of Time-Weighted Average Cmax).





AUC0-24, area under the plasma concentration-time curve from time 0 to 24 hours; CV, cardiovascular; N, subjects at risk; Probability, cumulative probability.

Source: The Applicant's E-R Report # 05D7SZ (Figure 4 and 5).

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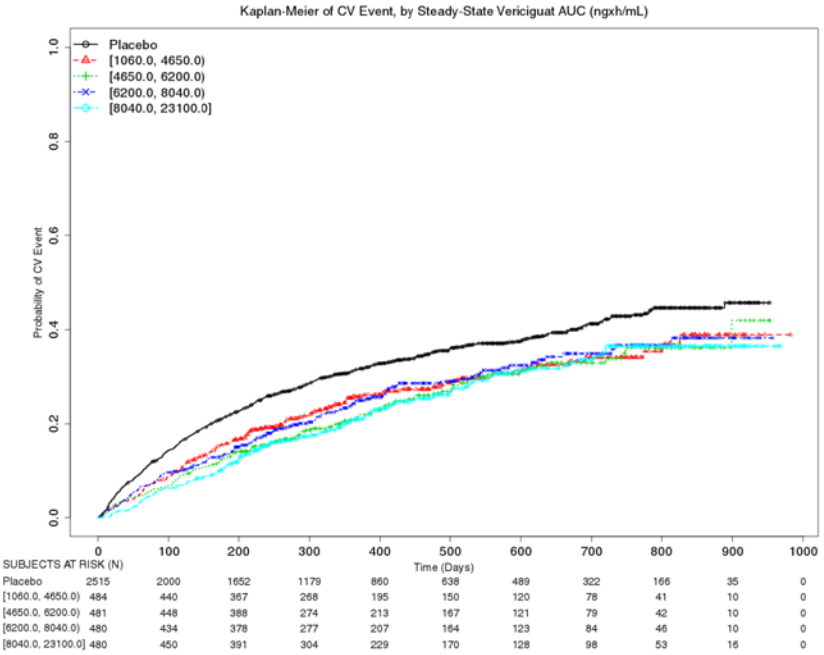
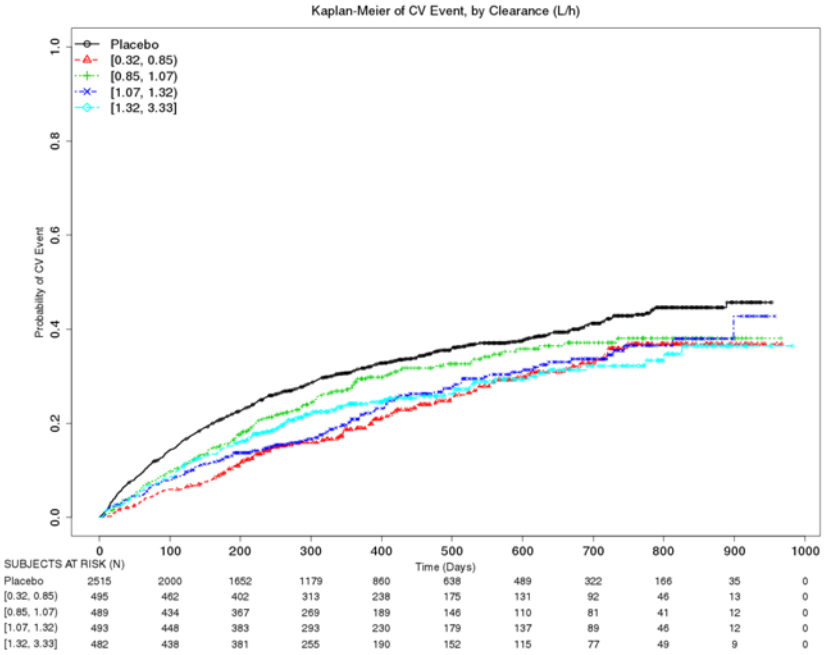
Figure 13 Kaplan-Meier Plot of Probability of Cardiovascular Event Versus Time (top: Quartiles of Steady-State AUC0-24 and bottom: Quartiles of Apparent Clearance).





AUC0-24, area under the plasma concentration-time curve from time 0 to 24 hours; CV, cardiovascular; N, subjects at risk; Probability, cumulative probability. Note: [or] indicates respective endpoint is included in the interval and (or) indicates respective endpoint is not included in the interval.

Source: The Applicant's E-R Report # 05D7SZ (Figure 9 and 8).

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Table 16 Summary of Evaluation of Time-Weighted Average Vericiguat Exposure Measures for the Exposure-Response Time to Cardiovascular Event Survival Analysis.

Model	Formula	Number of Events	Number of Parameters	Deviance	df	*P* value	Log Likeli-hood
Time-Weighted Average Vericiguat AUC_{0-24} (µg × h/mL)	Surv(AVAL, EVENT) ~ AVGAUCT.MCG	1322	1	20970	1	< 0.0001	-10487.3
Time-Weighted Average Vericiguat C_{max} (ng/mL)	Surv(AVAL, EVENT) ~ AVGCMAX	1322	1	20970	1	< 0.0001	-10485.7

AUC0-24, area under the plasma concentration-time curve from time 0 to 24 hours; Cmax, maximum concentration; df, degrees of freedom; P, probability.

Source: The Applicant's E-R Report # 05D7SZ (Table 14).

Following the inclusion of effect of vericiguat exposure into the base E-R model, the influence of covariates on the hazard of CV events was evaluated. The full model developed using time-weighted average AUC0-24 as the exposure metric is described below (**Table 17**). The sensitivity analysis of efficacy (512 subjects strictly on 10 mg) is provided in **Table 19**.

Table 17 Parameter Estimates and Standard Errors for the Exposure-Response Full Model for Time to Cardiovascular Events (Time-Weighted Average AUC0-24)

Variable	Coefficient	SE	RSE	*P* value	Hazard Ratio	Lower 95% CI	Upper 95% CI	Hazard Ratio (95% CI)
Time-Weighted Average Vericiguat AUC_{0-24} (µg × h/mL)	-0.08353	0.008956	10.72	0	0.9199	0.9039	0.9362	0.9199 (0.9039, 0.9362)
Quartiles of NT-proBNP Q2[a]	0.2762	0.09018	32.65	0.002194	1.318	1.105	1.573	1.318 (1.105, 1.573)
Quartiles of NT-proBNP Q3[a]	0.5408	0.08723	16.13	5.66E-10	1.717	1.448	2.038	1.717 (1.448, 2.038)
Quartiles of NT-proBNP Q4[a]	0.8119	0.08701	10.72	0	2.252	1.899	2.671	2.252 (1.899, 2.671)
Quartiles of NT-proBNP Missing[a]	0.2978	0.151	50.69	0.04854	1.347	1.002	1.811	1.347 (1.002, 1.811)
NYHA Class II[b]	-1.901	0.7112	37.4	0.007508	0.1494	0.03706	0.6021	0.1494 (0.03706, 0.6021)
NYHA Class III[b]	-1.625	0.7112	43.77	0.02233	0.1969	0.04886	0.7938	0.1969 (0.04886, 0.7938)
NYHA Class IV[b]	-0.6782	0.733	108.1	0.3549	0.5076	0.1207	2.135	0.5076 (0.1207, 2.135)
eGFR < 30 mL/min/1.73 m^2[c]	0.597	0.08704	14.58	6.98E-12	1.817	1.532	2.154	1.817 (1.532, 2.154)
eGFR 30 to ≤ 60 mL/min/1.73 m^2[c]	0.2013	0.06136	30.47	0.001033	1.223	1.084	1.379	1.223 (1.084, 1.379)
eGFR Missing[c]	0.1941	0.2455	126.5	0.4291	1.214	0.7505	1.964	1.214 (0.7505, 1.964)
Index Event of Hospitalization Within 3 Months Prior[d]	0.3531	0.08444	23.92	2.90E-05	1.423	1.206	1.68	1.423 (1.206, 1.68)
Index Event of Hospitalization 3 to 6 Months Prior[d]	-0.00728	0.1072	1473	0.9459	0.9927	0.8047	1.225	0.9927 (0.8047, 1.225)

AUC0-24, area under the plasma concentration-time curve from time 0 to 24 hours; CI, confidence interval; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; P, probability; Q, quartile; RSE, relative standard error; SE, standard error. [a] The reference category is Q1 of NT-proBNP. [b] The reference category is NYHA Class I. [c] The reference category is normal eGFR > 60 mL/min/1.73 m2. [d] The reference category is intravenous diuretic within 3 months of randomization.

Source: The Applicant's E-R Report # 05D7SZ (Table 17).

Reference ID: 4722292

Table 18 Parameter Estimates and Standard Errors for the Exposure-Response Full Model for Time to Cardiovascular Events (Daily AUC0-24)

Variable	Coefficient	SE	RSE	*P* value	Hazard Ratio	Lower 95% CI	Upper 95% CI	Hazard Ratio (95% CI)
Vericiguat AUC_{0-24} (µg × h/mL)	-0.1054	0.01439	13.66	2.49E-13	0.9	0.875	0.9258	0.9 (0.875, 0.9258)
Interaction Between Vericiguat AUC_{0-24} and Time	0.0001428	4.55E-05	31.83	0.001681	1	1	1	1 (1, 1)
Quartiles of NT-proBNP Q2[a]	0.2717	0.09017	33.19	0.002589	1.312	1.1	1.566	1.312 (1.1, 1.566)
Quartiles of NT-proBNP Q3[a]	0.5382	0.08722	16.21	6.80E-10	1.713	1.444	2.032	1.713 (1.444, 2.032)
Quartiles of NT-proBNP Q4[a]	0.8093	0.08701	10.75	0	2.246	1.894	2.664	2.246 (1.894, 2.664)
Quartiles of NT-proBNP Missing[a]	0.3038	0.1509	49.66	0.04402	1.355	1.008	1.821	1.355 (1.008, 1.821)
NYHA Class II[b]	-1.912	0.7112	37.19	0.007167	0.1477	0.03665	0.5954	0.1477 (0.03665, 0.5954)
NYHA Class III[b]	-1.638	0.7113	43.43	0.02131	0.1944	0.04824	0.7838	0.1944 (0.04824, 0.7838)
NYHA Class IV[b]	-0.6782	0.733	108.1	0.3548	0.5075	0.1206	2.135	0.5075 (0.1206, 2.135)
eGFR < 30 mL/min/1.73 m^2[c]	0.594	0.08707	14.66	8.97E-12	1.811	1.527	2.148	1.811 (1.527, 2.148)
eGFR 30 to ≤ 60 mL/min/1.73 m^2[c]	0.1993	0.06135	30.79	0.001161	1.221	1.082	1.376	1.221 (1.082, 1.376)
eGFR Missing[c]	0.1885	0.2453	130.1	0.4421	1.207	0.7466	1.953	1.207 (0.7466, 1.953)
Index Event of Hospitalization Within 3 Months Prior[d]	0.355	0.08443	23.78	2.62E-05	1.426	1.209	1.683	1.426 (1.209, 1.683)
Index Event of Hospitalization 3 to 6 Months Prior[d]	-0.0141	0.1072	760.2	0.8953	0.986	0.7992	1.217	0.986 (0.7992, 1.217)

AUC0-24, area under the plasma concentration-time curve from time 0 to 24 hours; CI, confidence interval; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; P, probability; Q, quartile; RSE, relative standard error; SE, standard error. [a] The reference category is Q1 of NT-proBNP. [b] The reference category is NYHA Class I . [c] The reference category is normal eGFR > 60 mL/min/1.73 m^2. [d] The reference category is intravenous diuretic within 3 months of randomization.

Source: The Applicant's E-R Report # 05D7SZ (Table 29).

Table 19 Parameter Estimates and Standard Errors for the Final Exposure-Response Model for Time to Cardiovascular Events (Subjects Strictly Administered 10 mg After Day 56 - Daily AUC0-24 Records as the Exposure Metric).

Variable	Coefficient	SE	RSE	*P* value	Hazard Ratio	Lower 95% CI	Upper 95% CI	Hazard Ratio (95% CI)
Vericiguat AUC_{0-24} (µg × h/mL)	-0.06137	0.05749	93.68	0.2857	0.9405	0.8403	1.053	0.9405 (0.8403, 1.053)
Interaction Between Vericiguat AUC_{0-24} and Time	0.000179	0.000176	98.26	0.3088	1	0.9998	1.001	1 (0.9998, 1.001)
Quartiles of NT-proBNP Q2[a]	0.03301	0.275	833.2	0.9045	1.034	0.6029	1.772	1.034 (0.6029, 1.772)
Quartiles of NT-proBNP Q3[a]	0.2915	0.2749	94.31	0.289	1.338	0.7809	2.294	1.338 (0.7809, 2.294)
Quartiles of NT-proBNP Q4[a]	0.7031	0.2689	38.25	0.008944	2.02	1.192	3.422	2.02 (1.192, 3.422)
Quartiles of NT-proBNP Missing[a]	0.1023	0.4859	474.9	0.8332	1.108	0.4274	2.871	1.108 (0.4274, 2.871)
NYHA Class III and IV[b]	0.003463	0.1786	5156	0.9845	1.003	0.7071	1.424	1.003 (0.7071, 1.424)
eGFR < 30 mL/min/1.73 m^2[c]	0.9463	0.2452	25.91	0.000114	2.576	1.593	4.165	2.576 (1.593, 4.165)
eGFR 30 to ≤ 60 mL/min/1.73 m^2[c]	0.2189	0.2033	92.85	0.2815	1.245	0.8357	1.854	1.245 (0.8357, 1.854)
eGFR Missing[c]	0.8892	0.646	72.65	0.1687	2.433	0.686	8.631	2.433 (0.686, 8.631)
Index Event of Hospitalization Within 3 Months Prior[d]	0.4688	0.2059	43.91	0.02277	1.598	1.067	2.393	1.598 (1.067, 2.393)

AUC0-24, area under the plasma concentration-time curve from time 0 to 24 hours; CI, confidence interval; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; P, probability; Q, quartile; RSE, relative standard error; SE, standard error. [a] The reference category is Q1 of NT-proBNP. [b] The reference category is NYHA Class I + II. [c] The reference category is normal eGFR > 60 mL/min/1.73 m^2. [d] The reference category is intravenous diuretic within 3 to 6 months of randomization.

Source: The Applicant's E-R Report # 05D7SZ (Table 33).

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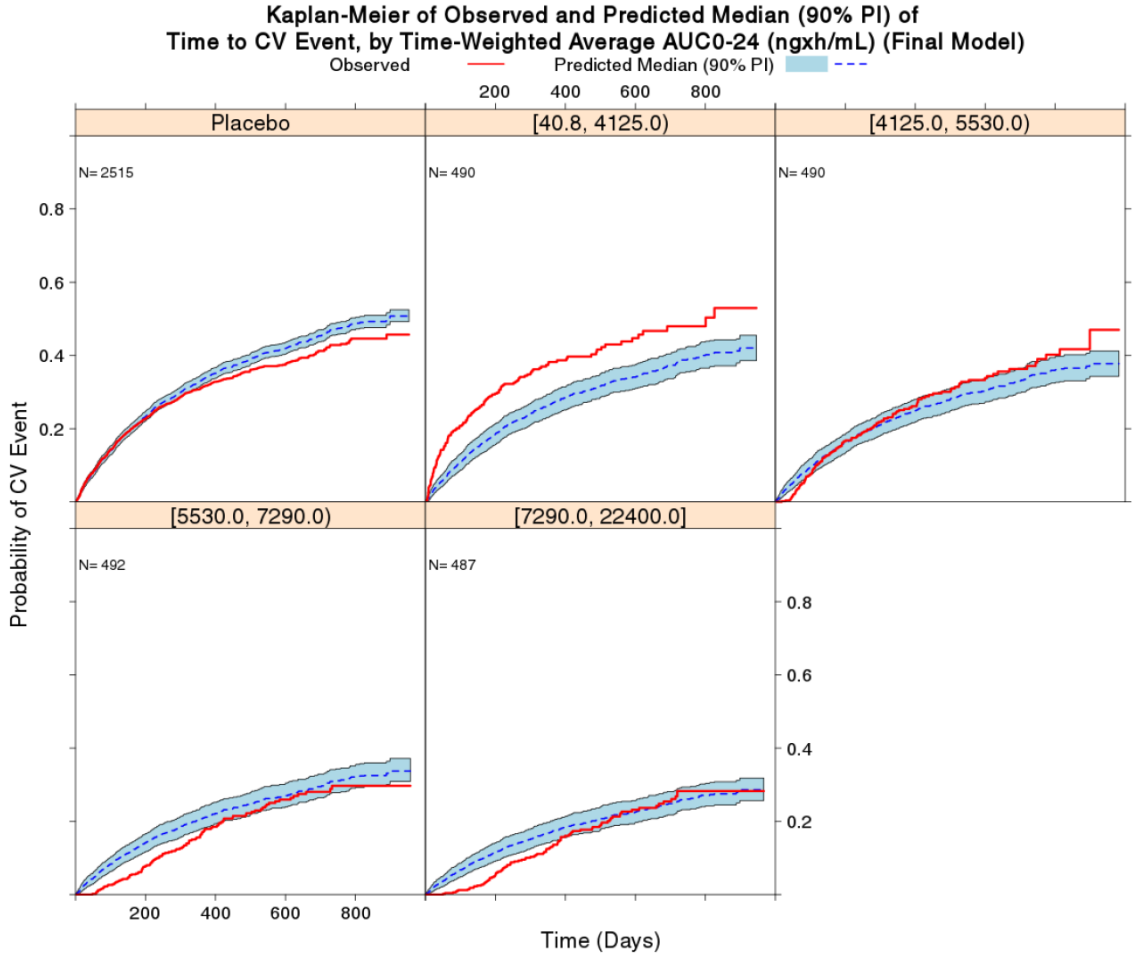
A VPC was performed using the final E-R model for time to composite CV outcome.

Figure 14 Visual Predictive Check Plot of the Simulated Percentiles of Subjects with Cardiovascular Events Versus Days with Kaplan-Meier Estimates of the Observed Data Overlaid, by Placebo and Quartiles of Time-Weighted Average Vericiguat Exposure.

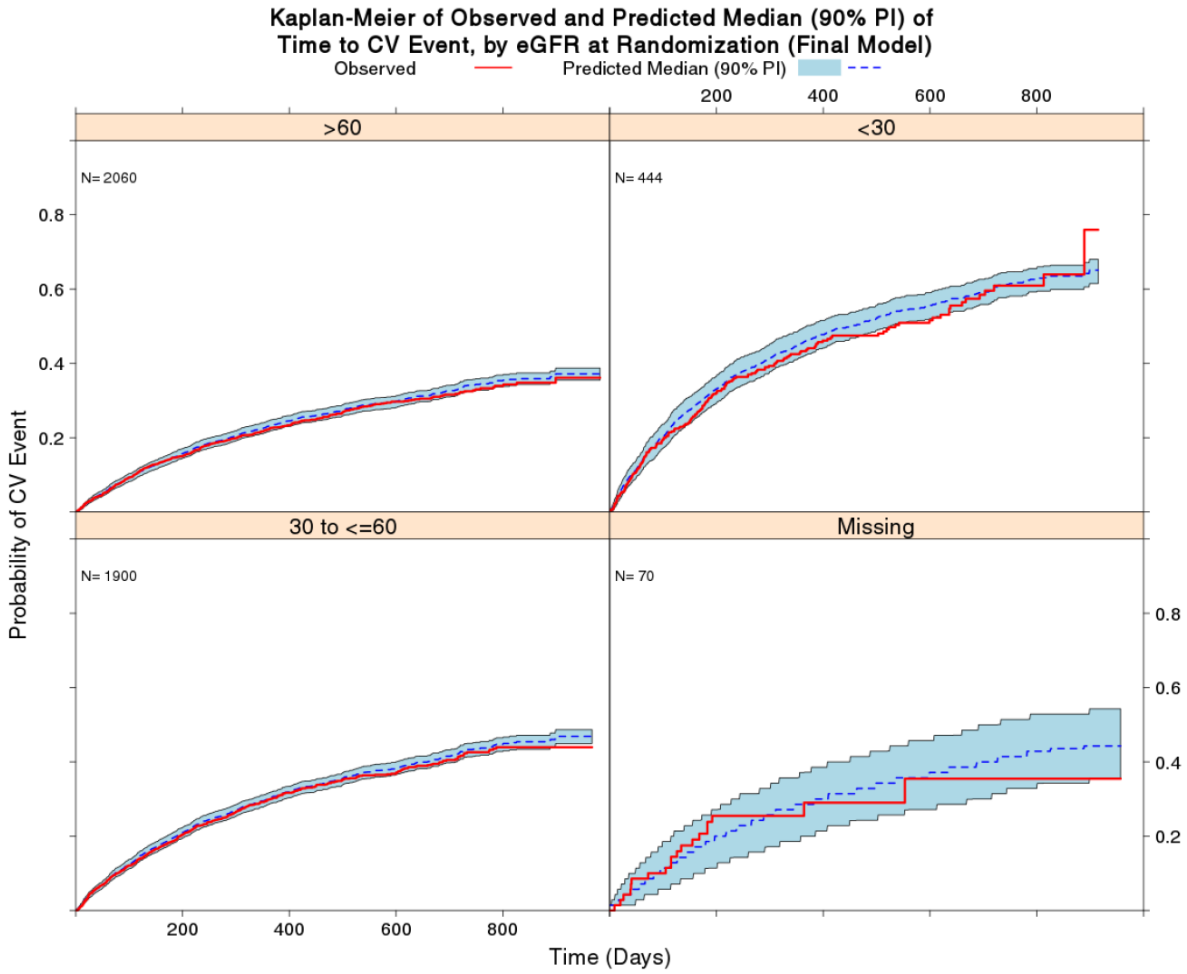


AUC0-24, area under the plasma concentration-time curve from time 0 to 24 hours; CV, cardiovascular; N, number of records; PI, prediction interval; Probability, cumulative probability. Note: [or] indicates respective endpoint is included in the interval and (or) indicates respective endpoint is not included in the interval.

Source: The Applicant's E-R Report # 05D7SZ (Figure 14).

Reference ID: 4722292

Figure 15 Visual Predictive Check Plot of the Simulated Percentiles of Subjects with Cardiovascular Events Versus Days with Kaplan-Meier Estimates of the Observed Data Overlaid, by eGFR Categories - Time-Weighted Average AUC0-24 Per Subject as the Exposure Metric.



CV, cardiovascular; eGFR, estimated glomerular filtration rate; N, number of records; PI, prediction interval; Probability, cumulative probability

Source: The Applicant's E-R Report # 05D7SZ (Figure 15).

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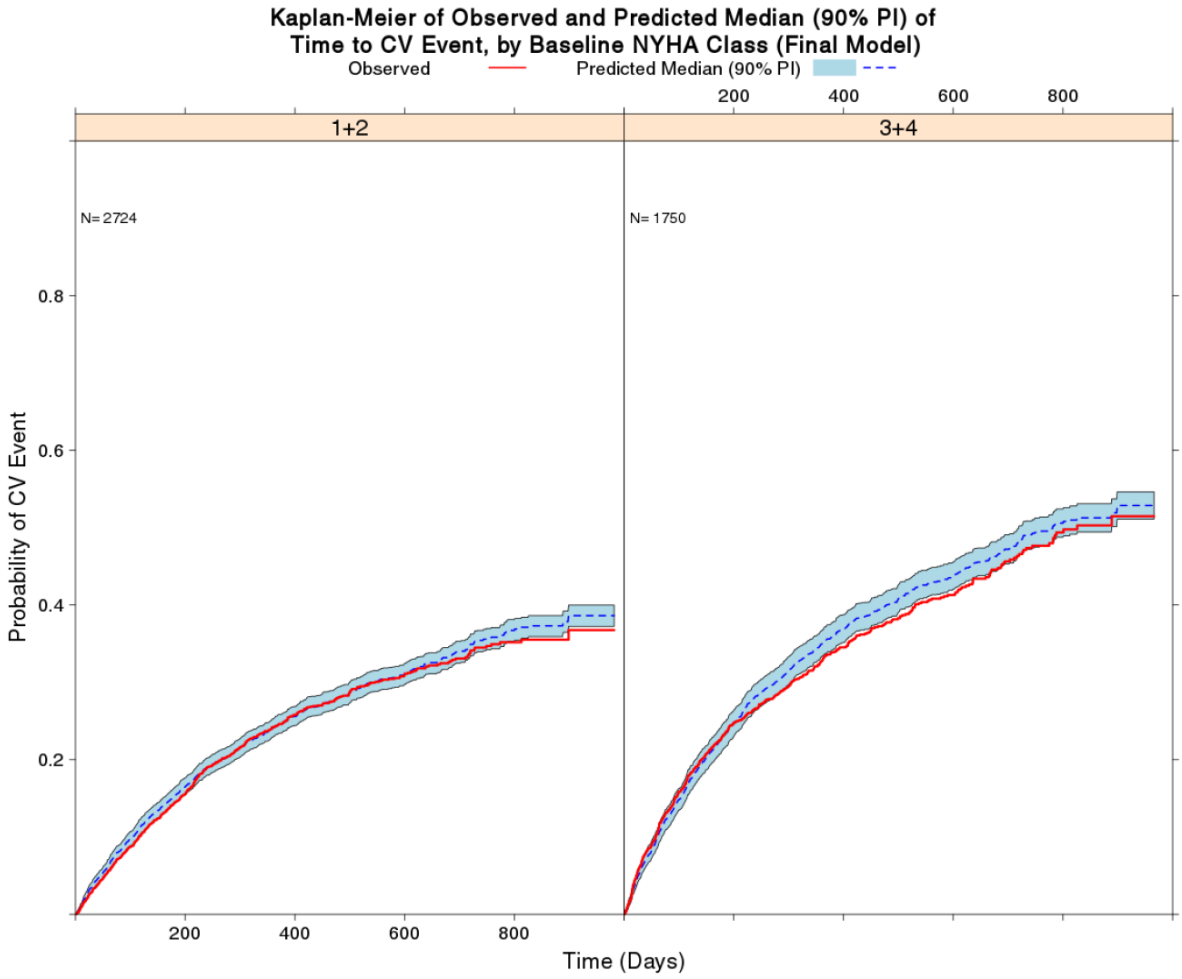
Figure 16 Visual Predictive Check Plot of the Simulated Percentiles of Subjects with Cardiovascular Events Versus Days with Kaplan-Meier Estimates of the Observed Data Overlaid, by NYHA Class - Time-Weighted Average AUC0-24 Per Subject as the Exposure Metric.



CV, cardiovascular; N, number of records; NYHA, New York Heart Association; PI, prediction interval; Probability, cumulative probability.

Source: The Applicant's E-R Report # 05D7SZ (Figure 17).

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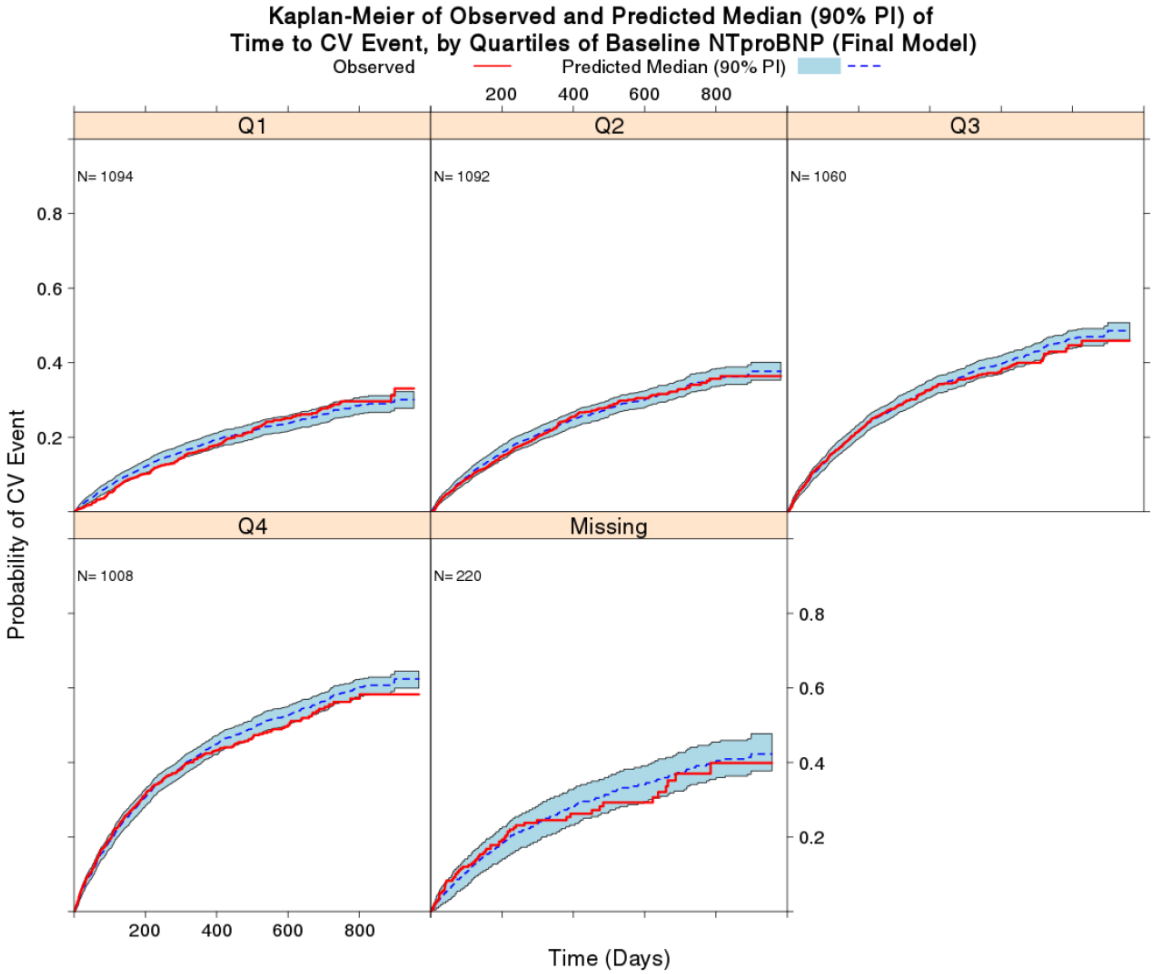
Figure 17 Visual Predictive Check Plot of the Simulated Percentiles of Subjects with Cardiovascular Events Versus Days with Kaplan-Meier Estimates of the Observed Data Overlaid, by Quartiles of Baseline NT-proBNP - Time-Weighted Average AUC0-24 Per Subject as the Exposure Metric.



CV, cardiovascular; N, number of records; NT-proBNP, N-terminal pro b-type natriuretic peptide; PI, prediction interval; Probability, cumulative probability; Q, quartile.

Source: The Applicant's E-R Report # 05D7SZ (Figure 18).

The overall conclusion from exposure–efficacy analyses using different exposure metrics is that the differences across the range of vericiguat exposure observed in VICTORIA likely did not influence efficacy in subjects with HFrEF.

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Systolic Blood Pressure

Exploratory E-R analyses of longitudinal SBP measures were performed on data collected from subjects with available vericiguat exposure estimates (and placebo) in the Phase 3 study. Previously, similar analysis was also performed for Phase 3 study (see Section 3.3.2).

For VICTORIA, the Applicant created 2 datasets – 1) SBP measurements on Day 1 at 2 hours post-dose including 4388 SBP measures from 4388 subjects (including placebo and vericiguat) and 2) SBP measurements post Day 1 (a total of 28,098 SBP measurements from Day 14 or 28 visits or Weeks 16 to 128 for 4474 subjects). Summaries of vericiguat exposures on Day 1 for SBP measurements collected 2 hours post-dose on Day 1 are provided in **Table 20**.

Table 20 Summary Statistics of Systolic Blood Pressure Measures Collected 2 Hours Post-Dose on Day 1 (by dose)

Pharmacodynamic Endpoint	Statistic	Dose (mg)			Overall
		0	2.5	5	
Change in SBP from Baseline (mm Hg)	Mean (SD)	-2.99 (9.85)	-3.77 (9.76)	-9.00 (NA)	-3.33 (9.82)
	Median	-3.00	-3.00	-9.00	-3.00
	Min, Max	-57.0, 38.0	-49.0, 38.0	-9.0, -9.0	-57.0, 38.0
	n	2464	1923	1	4388
SBP at Baseline (mm Hg)	Mean (SD)	121.47 (15.80)	121.55 (15.43)	119.00 (NA)	121.50 (15.64)
	Median	119.00	119.00	119.00	119.00
	Min, Max	91.0, 216.0	88.0, 189.0	119.0, 119.0	88.0, 216.0
	n	2464	1923	1	4388

Max, maximum; Min, minimum; n, number of subjects; SBP, systolic blood pressure; SD, standard deviation.

Source: The Applicant's E-R Report # 05D7SZ (Table 39).

Similarly, summaries of vericiguat exposures on the day of SBP measurements (excluding the 2-hour post-dose measures on Day 1) is provided in **Table 21**.

Table 21 Summary Statistics of Systolic Blood Pressure Measures (by dose; excluding 2-h post-dose measurement on Day 1)

Pharmacodynamic Endpoint	Statistic	Dose (mg)				Overall n = 4474
		0 mg n = 2823	2.5 mg n = 1957	5 mg n = 1719	10 mg n = 1720	
Change in SBP From Baseline (mm Hg)	Mean (SD)	-1.14 (15.69)	-5.04 (13.82)	-2.84 (13.96)	-0.30 (16.28)	-1.30 (15.64)
	Median	-1.00	-6.00	-3.00	0.00	-2.00
	Min, Max	-75.0, 84.0	-65.0, 47.0	-80.0, 62.0	-67.0, 92.0	-80.0, 92.0
	N	12980	1410	2389	6845	23624
SBP at Baseline (mm Hg)	Mean (SD)	121.80 (15.64)	119.40 (15.26)	120.41 (15.00)	123.52 (15.47)	121.82 (15.55)
	Median	119.00	117.00	118.00	121.00	119.00
	Min, Max	88.0, 216.0	88.0, 189.0	90.0, 189.0	88.0, 189.0	88.0, 216.0
	N	15502	3361	2390	6845	28098

Max, maximum; Min, minimum; N, number of records; n, number of subjects; NA, not applicable; SBP, systolic blood pressure; SD, standard deviation.

Source: The Applicant's E-R Report # 05D7SZ (Table 38).

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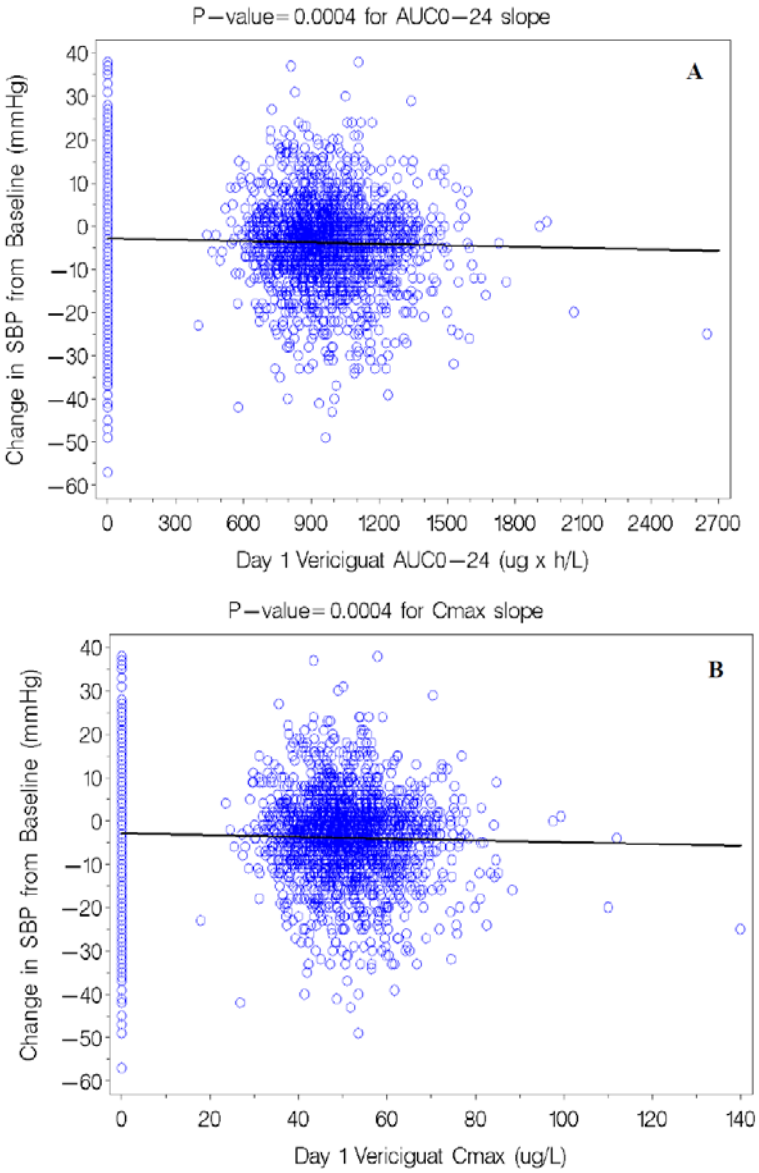
The Applicant's analysis indicated slight negative correlation between SBP versus vericiguat exposure for 2-h post dose data on Day 1. Similarly, the Applicant used linear regression model to explore relationship between the change in SBP measurements from baseline and vericiguat exposure.

Figure 18 Scatterplots of Change in Systolic Blood Pressure at the 2-Hour Post-Dose Day 1 Versus Vericiguat Exposure (Top: AUC0-24 and Bottom: Cmax) Using Linear Regression.



AUC0-24, area under the plasma concentration-time curve from time 0 to 24 hours; Cmax, maximum concentration; SBP, systolic blood pressure.

Source: The Applicant's E-R Report # 05D7SZ (Figure 37).

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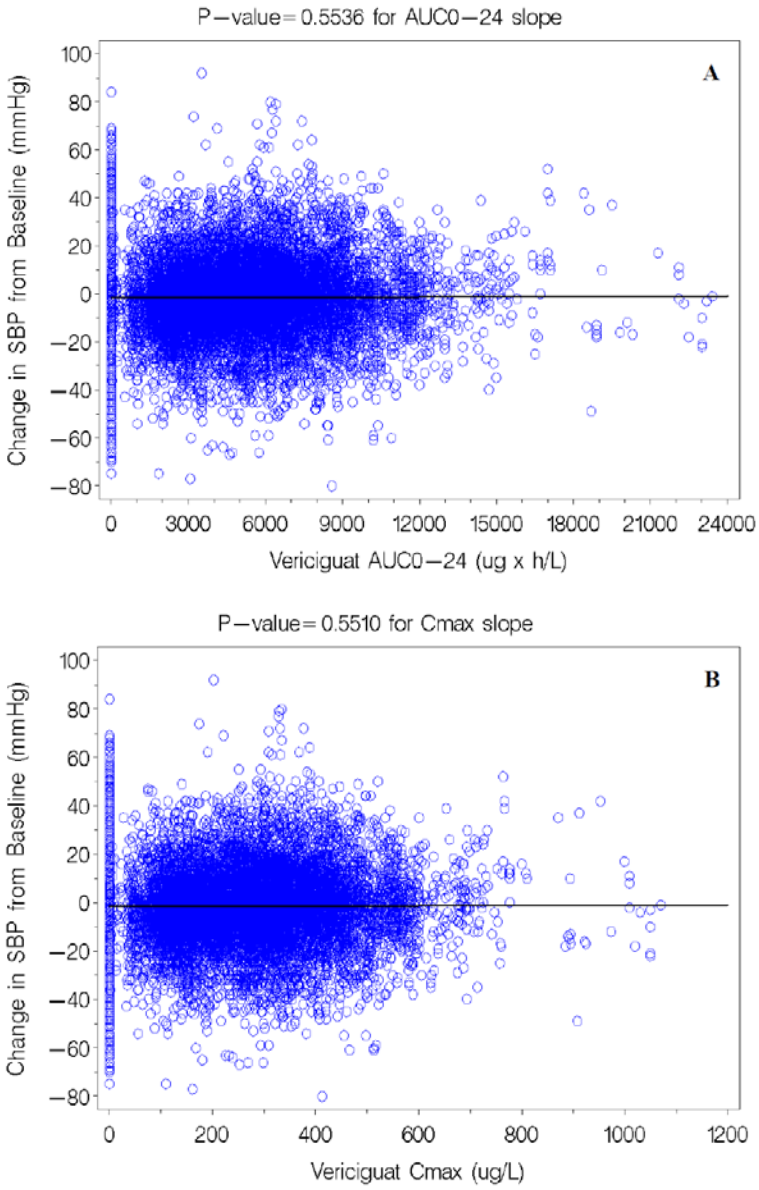
Following Day 1, there was no E-R relationship evident between SBP versus vericiguat exposure post Day 1 overall or on Days 14 or 28 or Weeks 16 to 128 (**Figure 19**).

Figure 19 Scatterplots of Change in Systolic Blood Pressure Versus Vericiguat Exposure (Top: AUC0-24 and Bottom: Cmax) Using Linear Regression.



AUC0-24, area under the plasma concentration-time curve from time 0 to 24 hours; Cmax, maximum concentration; SBP, systolic blood pressure. Note: These graphs exclude SBP measures taken on Day 1 at 2 h post-dose.

Source: The Applicant's E-R Report # 05D7SZ (Figure 38).

Scatterplots of the Day 14 and Day 28 change in SBP versus vericiguat exposure measures are shown in **Figure 20** and **Figure 21**, respectively. Scatterplots of the Week 16 to 128 change in SBP versus vericiguat exposure measures are shown in **Figure 22**.

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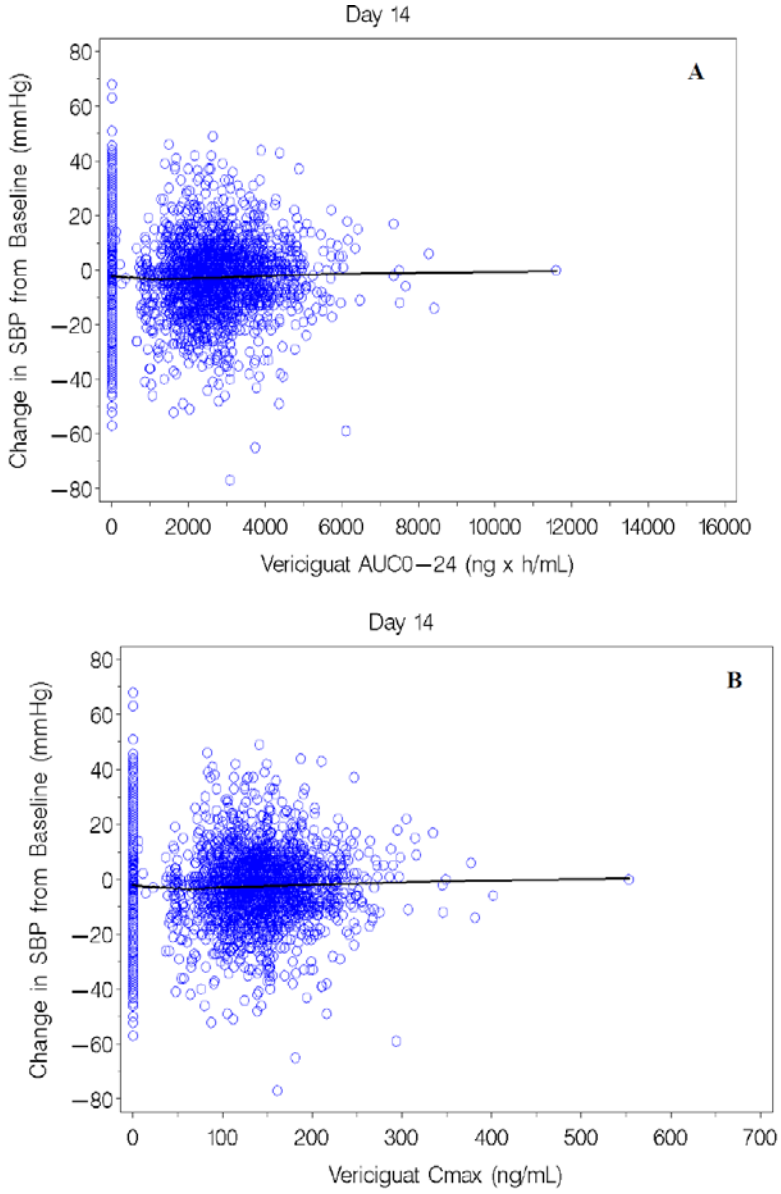
Figure 20 Scatterplots of Change in Systolic Blood Pressure on Day 14 Versus Vericiguat Exposure (Top: AUC0-24 and Bottom: Cmax) Using Linear Regression.

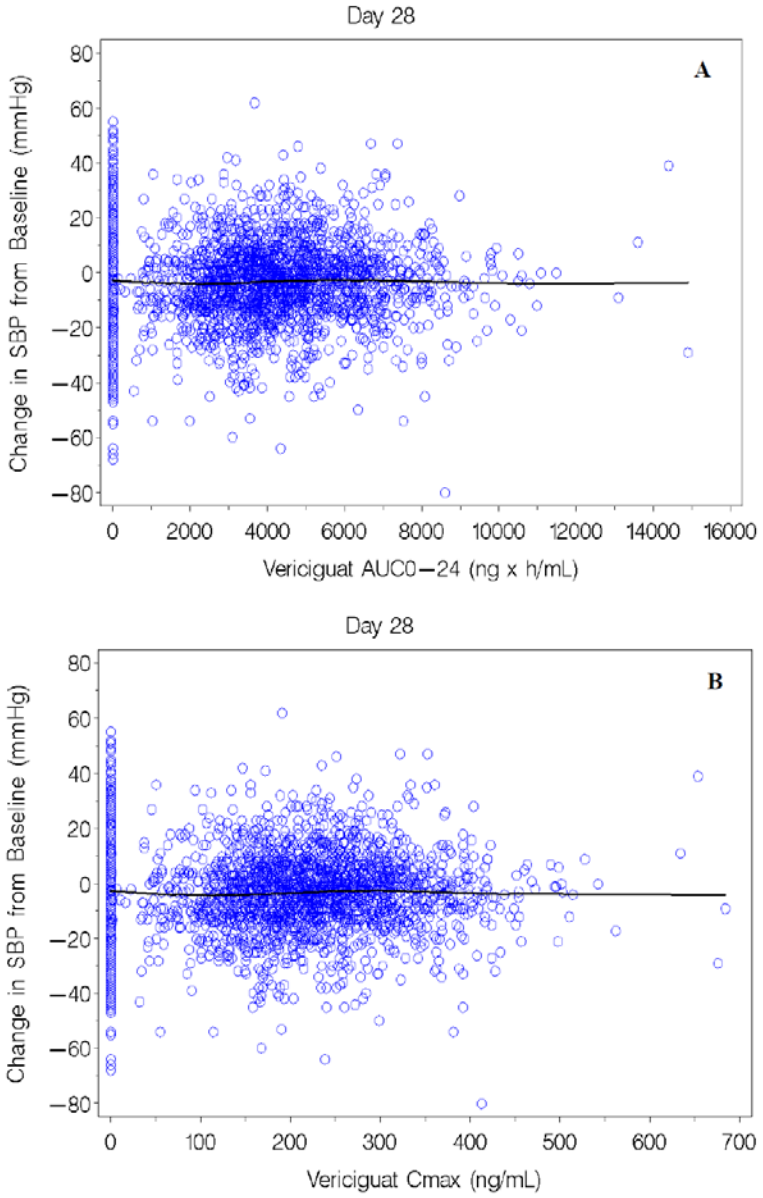


AUC0-24, area under the plasma concentration-time curve from time 0 to 24 hours; Cmax, maximum concentration; SBP, systolic blood pressure.

Source: The Applicant's E-R Report # 05D7SZ (Figure 40).

Reference ID: 4722292

Figure 21 Scatterplots of Change in Systolic Blood Pressure on Day 28 Versus Vericiguat Exposure (Top: AUC0-24 and Bottom: Cmax) Using Linear Regression.

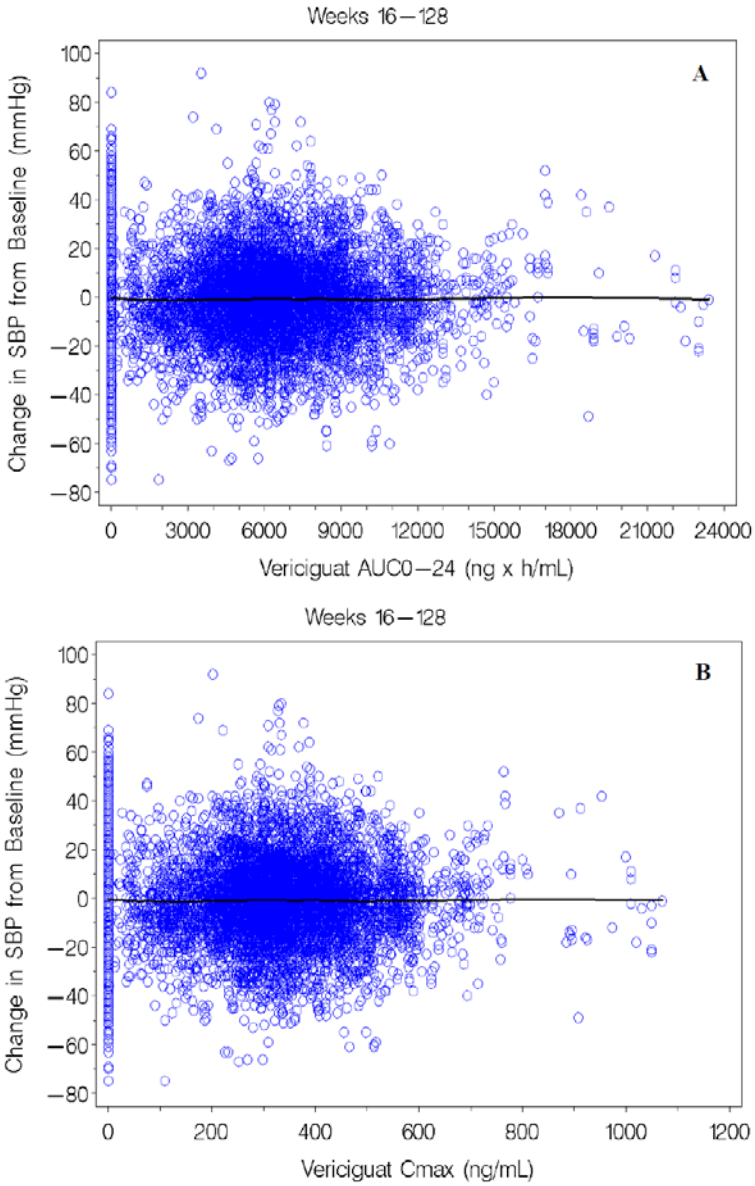


AUC0-24, area under the plasma concentration-time curve from time 0 to 24 hours; Cmax, maximum concentration; SBP, systolic blood pressure.

Source: The Applicant's E-R Report # 05D7SZ (Figure 41).

Reference ID: 4722292

Figure 22 Scatterplots of Change in Systolic Blood Pressure Between Week 16 and 128 Versus Vericiguat Exposure (Top: AUC0-24 and Bottom: Cmax) Using Linear Regression.



AUC0-24, area under the plasma concentration-time curve from time 0 to 24 hours; Cmax, maximum concentration; SBP, systolic blood pressure.

Source: The Applicant's E-R Report # 05D7SZ (Figure 42).

In summary, there was statistically significant correlation between higher vericiguat exposure and greater decrease in SBP from baseline at 2 hours after the first dose was administered on Day 1. However, there was no significant E-R relationship was found for SBP (on Day 14 or 28 or Weeks 16 to 128, and overall post Day 1).

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Reviewer's Comments:

The Applicant's E-R efficacy analysis is acceptable based on the model parameter estimates, associated uncertainties, and simulations for various scenarios. Considering a flexible titration-based dosing regimen, the Applicant utilized complimentary exposure metrics and also conducted sensitivity analysis using a subset of population who were strictly on 10 mg after Day 56, the final E-R model for time to composite CV outcome. In this population, vericiguat exposure was not seen as a significant predictor of the probability of CV events indicating the plateau of the E-R relationship.

The Applicant's E-R analysis for SBP indicated a statistically significant correlation between higher vericiguat exposure and greater decrease in SBP from baseline at 2 hours after the first dose was administered on Day 1. However, there was no significant E-R relationship found for SBP on Day 14 or 28 or Weeks 16 to 128. These analyses are supportive of the proposed titration-based dosing regimen.

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4.3 Physiologically based Pharmacokinetic (PBPK) Modeling Review

NDA Number	214377
Generic Name	Vericiguat
Trade Name	VERQUVO™
Submission Type	505(b)(1)
Applicant	Merck
Dosage Form and Strengths	Oral tablets, 2.5 mg, 5 mg and 10 mg
Proposed Indication	Indicated to reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for heart failure or need for outpatient IV diuretics, in adults with symptomatic chronic HF and ejection fraction less than 45 %
Proposed Dose Regimen	o The recommended starting dose of TRADEMARK is 2.5 mg once daily, taken with food. o Double the dose of TRADEMARK approximately every 2 weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient.
Primary PBPK Reviewer	Jianghong Fan, Ph.D.
Secondary PBPK Reviewer	Yuching Yang, Ph.D.

4.3.1 Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's following PBPK reports to support the intended uses.

- 05FWQK_PBPK for vericiguat and its metabolite M-1: Exploratory population pharmacokinetic analysis of the pharmacokinetics of vericiguat and its metabolite M-1 using physiologically-based pharmacokinetic (PBPK) modelling;
- 058S33_PBPK of vericiguat and its metabolite M-1: Exploratory physiologically based pharmacokinetic (PBPK) simulations to evaluate intrinsic and extrinsic factors on pharmacokinetics of vericiguat and its metabolite M-1.

The Division of Pharmacometrics has reviewed the PBPK reports, supporting modeling files, and the Applicant's responses to the FDA's information requests (IRs) submitted on September 30, 2020, October 13, 2020, and November 18, 2020 and concluded the following:

- The vericiguat PBPK model is adequate to predict the vericiguat PK profiles following a single dose administration (0.5, 1, 2.5, 5, 7.5, 10 and 15 mg) and multiple does administration (1.5, 5 and 10 mg, qd and 5 mg bid) in healthy subjects.
- The vericiguat and M-1 PBPK model is inadequate to predict the M-1 PK profiles following administration of vericiguat in healthy subjects.
- The vericiguat PBPK model is adequate to predict the effect of mefenamic acid (an UGT1A9 inhibitor) on vericiguat PK following multiple dose administration of mefenamic acid (500 mg loading dose followed by 200 mg every 6 hours) and a single dose administration of

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vericiguat (2.5 mg). Model predicted vericiguat geometric mean AUC ratio was less than 1.35 with mefenamic acid in healthy subjects.

- Mefenamic acid cannot be considered as a strong UGT1A9 inhibitor, results from the DDI of vericiguat with mefenamic acid should not be extrapolated to other UGT1A9 inhibitors without further evaluation.
- The vericiguat PBPK model is adequate to predict the effect of atazanavir (an UGT1A1 inhibitor) on vericiguat PK following multiple dose administration of atazanavir (400 mg qd) and a single dose administration of vericiguat (10 mg). Model predicted vericiguat geometric mean AUC ratio was less than 1.27 with atazanavir in healthy subjects.
- It is recommended conducting in vitro studies to identify the transporters responsible for the active tubular secretion of M-1 (such as MRPs) in the kidney and biliary excretion in the liver and evaluate the potential inhibitory effects of vericiguat and M-1 on the identified transporters.
- The Applicant has completed the investigation into whether M-1 is a substrate of efflux transporters MRP2 and MPR4. The Applicant has also completed the assessment of the inhibitory potential of vericiguat and M-1 towards MRP2 and MRP4 upon demonstration that M-1 is a substrate of these transporters.

4.3.2 Applicant's PBPK Modeling Effort

PBPK software

PK-Sim V7.1 and MoBi V7.1 (Open Systems Pharmacology) were used by the Applicant to develop the PBPK models and DDI predictions. The reviewer used the PK-Sim V 9.0 for analyses.

Model development

Vericiguat and M-1

Absorption

A human whole body PBPK model was developed to characterize the PK of vericiguat and its major metabolite M-1 in plasma, urine and feces. Weibull cumulative distribution functions were fitted to the clinical observed PK data to obtain the dissolution parameters "dissolution time (50% dissolved" and the "dissolution shape" of the tablet formulations for 1.25, 2.5, 5 and 10 mg tablets. Intestinal permeability (4.11E-5 cm/min and 5.78E-7 cm/min) and organ permeability (4.48E-3 cm/min and 4.99E-6 cm/min) were estimated in PK-Sim for vericiguat and M-1 based on the physicochemical properties, respectively.

Distribution

The plasma protein binding for vericiguat and M-1 in human is about 0.978 and 0.983, respectively.

PK-Sim PBPK-model consists of 18 organs and tissues (arterial and venous blood, adipose tissue, brain, lung, bone, gonads, heart, kidneys, large intestine, liver, muscle, portal vein, pancreas, skin, small intestine, spleen and stomach). The standard PK-Sim 3-compartment

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model (intracellular, interstitial and vascular space) with a single permeation barrier between the interstitial and intracellular space in each organ was used to characterize the distribution of vericiguat and M-1. The partition coefficients of vericiguat and M-1 were estimated using Rodgers and Rowland's method.

Metabolism

In vitro studies indicated that UGT1A9, UGT1A1, CYP1A1 and CYP3A4 are the enzymes involved in the metabolism of vericiguat. UGT1A9 and UGT1A1 are the enzymes responsible for the formation of N-glucuronide of vericiguat, M-1. In the liver, glucuronidation is catalyzed by the UGT1A1 and UGT1A9, whereas in the kidney, glucuronidation is almost exclusively mediated by UGT1A9 (PBPK report section 4.8.3). The relative hepatic contributions of UGT1A1 (0.4) and UGT1A9 (0.6) to the glucuronidation of vericiguat were derived from in vitro study (PH-41293). In vitro studies (such as Study PH39129) and in vivo DDI study with ketoconazole (Study 15812, P008) indicated minor contribution of CYP1A1 and CYP4A4 to the overall clearance of vericiguat (<10%). The $kcat,_{UGT1A1}$ and $kcat,_{UGT1A9}$ (tissue-independent turnover number) parameter values were estimated based on clinical PK data (Study 17114). As there is no indication for non-linear PK of vericiguat, linear kinetics was assumed by assigning a very high value (1000 μM) to the Km of UGT1A1 and UGT1A9. The relative contributions of CYP1A1 and CYP3A4 to the total oxidative metabolism were estimated based on the in vitro data (DMPK PH-39129). The fraction of oxidative metabolites relative to the total dose was estimated based on the mass balance study (Study PH-38512).

Elimination

Glomerular filtration in the kidneys was used to describe the passive filtration of vericiguat and M-1 from kidney blood into urine. Urinary recovery (6-8%) indicated that renal excretion of veriviguat is primarily driven by the passive glomerular filtration.

Vericiguat was reported in vitro to be a weak substrate of the transporter P-gp and BCRP with the efflux ratio of 6.9 and 10.8, respectively. P-gp and BCRP mediated clearance were incorporated in the vericiguat model. The relative contribution of P-gp and BCRP to vericiguat clearance was derived based on in vitro data. The efflux transport clearance was estimated based on the clinical PK study (Study 17114).

(b) (4)

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(b) (4)

Victim and perpetrator drug models

Mefenamic acid

Mefenamic acid is a UGT1A9 inhibitor. The mefenamic acid PBPK model was developed to evaluate the DDI between mefenamic acid and UGT1A9 substrates. An in vitro in-house Ki value (0.3 μM) of mefenamic acid for UGT1A9 was used in the model. The mefenamic acid PBPK model and evaluation report are available on the Open System Pharmacology website (https://github.com/Open-Systems-Pharmacology/Dapagliflozin-model). Representative model validation results were shown in ***Figure 24 A***. The mefenamic acid mediated inhibitory effect on UGT1A9 pathway was validated with clinical DDI study results with dapagliflozin. The DDI evaluation report is available on the Open System Pharmacology website (https://github.com/Open-Systems-Pharmacology/Mefenamic_acid-Dapagliflozin-DDI). The evaluation results were shown in **Table *22***.

Dapagliflozin

The dapagliflozin PBPK model was developed for the purpose of dapagliflozin acting as a UGT1A9 substrate. Dapagliflozin is predominantly metabolized by UGT1A9 in the liver and kidneys to the glucuronide metabolite. The relative contribution of UGT1A9 to the overall clearance of dapagliflozin was estimated to be 0.80. The dapagliflozin PBPK model and evaluation report are available on the Open System Pharmacology website (https://github.com/Open-Systems-Pharmacology/Dapagliflozin-model). Representative model validation results were shown in **Figure *24B***.

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Atazanavir

Atazanavir is a UGT1A1 inhibitor. The atazanavir PBPK model was developed to evaluate the DDI between atazanavir and UGT1A1 substrates. An in vitro in-house determined atazanavir Ki value (0.19 μM) for UGT1A1 was applied to incorporate the reversible UGT1A1 inhibition. The atazanavir PBPK model and evaluation report are available on the Open System Pharmacology website (https://github.com/Open-Systems-Pharmacology/Atazanavir-Model). Representative model validation results were shown in **Figure *24C.*** The atazanavir mediated inhibitory effect on UGT1A1 pathway was validated with clinical DDI study results with raltegravir. The DDI evaluation report is available on the Open System Pharmacology website (https://github.com/Open-Systems-Pharmacology/Atazanavir-Raltegravir-DDI). The evaluation results were shown in ***Table 22*** .

Raltegravir

The raltegravir PBPK model was developed for the purpose of raltegravir acting as a UGT1A1 substrate. Raltegravir is metabolized primarily by UGT1A1 and to a lesser extent by UGT1A9. The relative contributions of UGT1A1 and UGT1A9 to the overall clearance of raltegravir were estimated to be 0.61 and 0.27, respectively, after corrected for fraction of absorbed (0.36). The raltegravir PBPK model and evaluation report are available on the Open System Pharmacology website (https://github.com/Open-Systems-Pharmacology/Raltegravir-Model). Representative model validation results were shown in **Figure *24D***.

Figure 24 Verification of PBPK models of A) Mefenamic acid; B) Dapagliflozin; C) Atazanavir and D) Raltegravir

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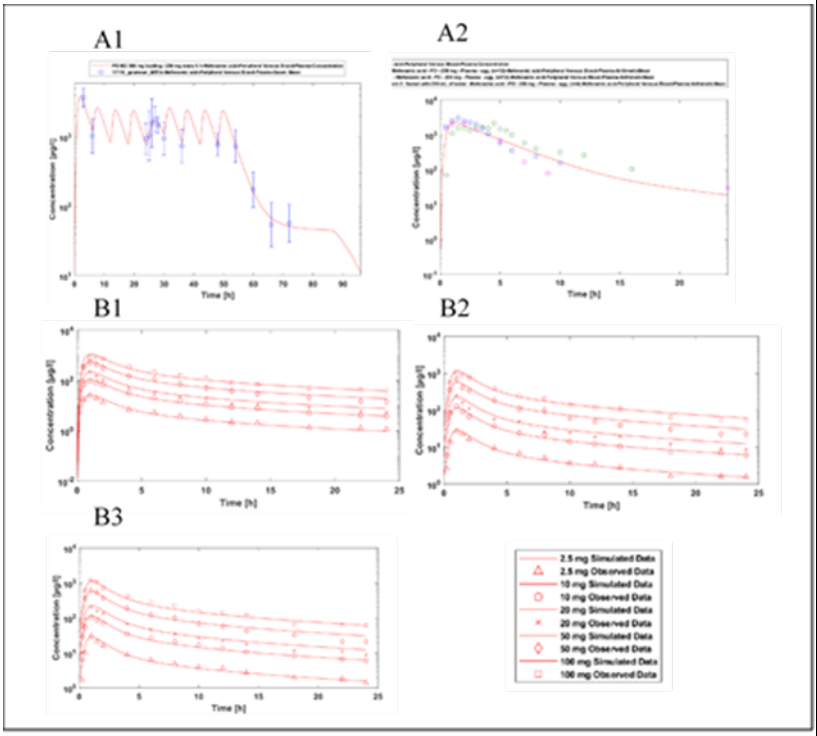

A. Mefenamic acid model validation with clinical PK data. A1: 500 mg oral loading dose followed by 250 mg oral every 6 hr (8 doses) under fed condition (Study 17116). A2: 250 mg single oral dose under fasted condition [2,3,4].

B. Dapagliflozin model validation with clinical PK data. B1, B2 and B3 represent dapagliflozin plasma PK profiles following multiple oral dose administration on day 1, day 7, and day 14, respectively[5].

[2] T Hamaguchi, D Shinkuma, Y Yamanaka, N Mizuno. Effects of food on absorption of mefenamic acid from two commercial capsules differing in bioavailability under the fasting state. J Pharmacobiodyn.1987 Jan;10(1):21-5.
[3] Mahadeo Mahadik, Sunil Dhaneshwar, Ravindra Bhavsar. A high performance liquid chromatography-tandem mass spectrometric method for the determination of mefenamic acid in human plasma: application to pharmacokinetic study. Biomed Chromatogr 2012 Oct;26(10):1137-42.
[4]Mohammad-Reza Rouini, Ali Asadipour, Yalda Hoseinzadeh Ardakani, Fakhredin Aghdasi. Liquid chromatography method for determination of mefenamic acid in human serum. J Chromatogr B Analyt Technol Biomed Life Sci. 2004 Feb 5;800(1-2):189-92.
[5]FDA Clinical Pharmacology Review for NDA 202293:
(https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/202293Orig1s000ClinPharmR.pdf)

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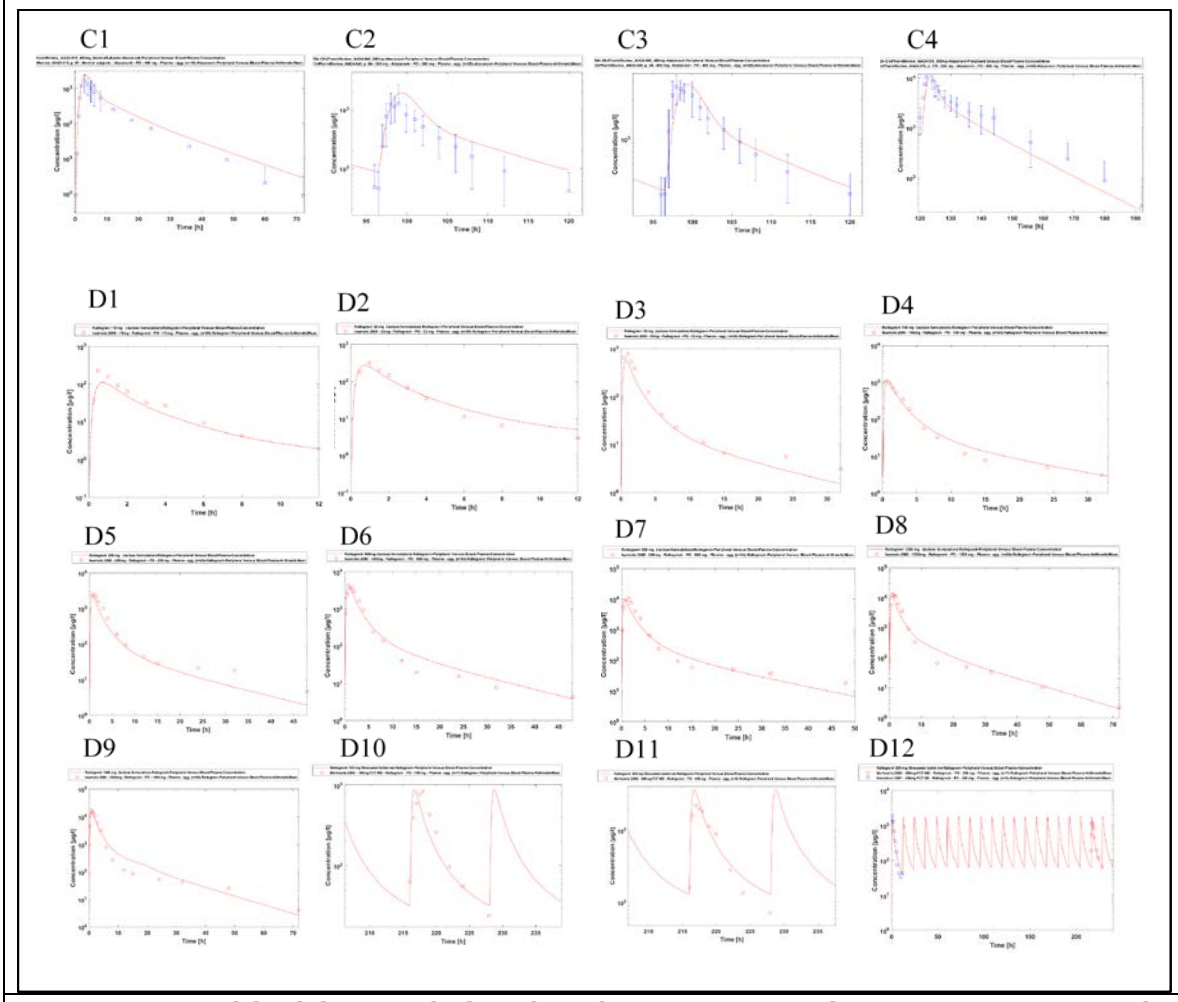

C. Atazanavir model validation with clinical PK data. C1, C2, C3 and C4 represent atazanavir plasma PK profiles following a single oral dose administration of 400 mg atazanavir, and multiple oral dose administrations of 200, 400 and 800 mg atazanavir, respectively[6].

D. Raltegravir model validation with clinical PK data. D1, D2, D3, D4, D5, D6, D7, D8, and D9 represent raltegravir plasma PK profiles following a single oral dose administration of 10, 25, 50, 100, 200, 400, 800, 1200, 1600 mg raltegravir, respectively [7]. D10, D11 and D12 represent raltegravir

[6] US Food and Drug Administration. Reyataz (atazanavir) capsules: Clinical Pharmacology and Biopharmaceutics Review, Application number: 21-567, 2002. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-567_Reyataz_BioPharmr_P1.pdf

[7] Iwamoto M, Wenning LA, Petry AS, Laethem M, De Smet M, Kost JT, Merschman. SA, Strohmaier KM, Ramael S, Lasseter KC, Stone JA, Gottesdiener KM, Wagner JA. Safety , tolerability, and pharmacokinetics of raltegravir after single and multiple doses in healthy subjects. Clin Pharmacol Ther. 2008 Feb;83(2):293-9. Epub 2007 Aug 22.

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plasma PK profiles following multiple oral dose administrations of 100[8], 400[9] and 200 mg[10] raltegravir, BID, respectively.

Data source: PBPK report 20871/PH41143

Table 22 Observed and simulated AUCR and CmaxR of dapagliflozin and raltegravir with and without perpetrators, mefenamic acid and atazanavir, respectively.

Perpetrator	Victim	Predicted AUC Ratio	Observed AUC Ratio	Pred/Obs AUC Ratio	Predicted CMAX Ratio	Observed CMAX Ratio	Pred/Obs CMAX Ratio	Reference
Atazanavir, 400 mg, PO	Raltegravir, PO	1.4925	1.72	0.86775	1.3576	1.53	0.8873	Iwamoto 2008
Atazanavir, 400 mg, PO	Raltegravir, PO	1.426	1.67	0.85387	1.3323	1.16	1.1485	Krishna 2016
Atazanavir, 400 mg, PO	Raltegravir, PO	1.444	1.72	0.83952	1.1171	1.37	0.81541	Neely 2010
Atazanavir, 400 mg, PO	Raltegravir, PO	1.5716	1.536	1.0232	1.3904	1.394	0.99739	Zhu 2010
Mefenamic Acid, 500 / 250 mg, PO	Dapagliflozin, PO	1.3378	1.51	0.88594	1.1561	1.13	1.0231	Kasichayanula 2013a

Data source: Table in Appendix AA5 qualification report UGT DDI inhibition in PBPK report 20871/PH41143

4.3.3 FDA's assessment

a) Mefenamic acid and atazanavir PBPK models are considered adequate for the purpose of acting as an inhibitor of UGT1A9 or UGT1A1. The dapagliflozin and raltegravir PBPK models are considered adequate for the purpose of acting as a substrate of UGT1A9 or UGT1A1 in DDI evaluation with UGT1A9 or UGT1A1 inhibitors.

b) (b) (4) [redacted] An information request was issued to conduct in vitro studies to identify the transporters responsible for the active tubular secretion (such as MRPs) in the kidney and biliary excretion in the liver. The potential inhibitory effects of vericiguat and M-1 on the identified transporters also need to be investigated.

[8] Martin Markowitz, Javier O Morales-Ramirez, Bach-Yen Nguyen, Colin M Kovacs, Roy T Steigbigel, David A Cooper, Ralph Liporace, Robert Schwartz, Robin Isaacs, Lucinda R Gilde, Larissa Wenning, Jing Zhao, Hedy Teppler. Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518, a novel inhibitor of HIV-1 integrase, dosed as monotherapy for 10 days in treatment-naive HIV-1-infected individuals. J Acquir Immune Defic Syndr. 2006 Dec 15;43(5):509-15.

[9] Martin Markowitz, Javier O Morales-Ramirez, Bach-Yen Nguyen, Colin M Kovacs, Roy T Steigbigel, David A Cooper, Ralph Liporace, Robert Schwartz, Robin Isaacs, Lucinda R Gilde, Larissa Wenning, Jing Zhao, Hedy Teppler. Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518, a novel inhibitor of HIV-1 integrase, dosed as monotherapy for 10 days in treatment-naive HIV-1-infected individuals. J Acquir Immune Defic Syndr. 2006 Dec 15;43(5):509-15.

[10] Kelem Kassahun, Ian McIntosh, Donghui Cui, David Hreniuk, Shelia Merschman, Kenneth Lasseter, Neal Azrolan, Marian Iwamoto, John A Wagner, Larissa A Wenning. Metabolism and disposition in humans of raltegravir (MK-0518), an anti-AIDS drug targeting the human immunodeficiency virus 1 integrase enzyme. Drug Metab Dispos. 2007 Sep;35(9):1657-63.

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c) Mefenamic acid is a highly plasma protein bound drug with a fu,b value of 0.02. Based on the in vitro determined Ki,u value of 0.3 μM and the clinically relevant plasma concentration (Cmax=2820 μg/L (Study p023mk1242), Cmax,u=0.23 μM), mefenamic acid is not a strong UGT1A9 inhibitor clinically. An information request was issued requesting the Applicant to conduct simulations to assess the DDI liability of vericiguat as a victim with a potential UGT1A9 inhibitor by assigning different fmUGT1A9 values in the vericiguat model.

d) Because mefenamic acid is not a strong UGT1A9 inhibitor, the change in AUCR of vericiguat with mefenamic acid is not sensitive to the change in fmUGT1A9 value, the clinical DDI study with mefenamic acid may not be used to verify the fmUGT1A9 for vericiguat, which was determined based on in vitro study results (Study PH-41293).

For the DDI of vericiguat with atazanavir, since there are no clinical DDI study data available for model validation, the uncertainty associated with the estimate of fmUGT1A1 for vericiguat and Ki value of atazanavir for UGT1A1 warrants further evaluation. The reviewer has conducted further evaluation based on the available clinical DDI study results as follows.

1. Firstly, the Ki value of mefenamic acid for UGT1A9 was refined to be 0.15 μM to match the observed AUCR of dapagliflozin with mefenamic acid which is 1.5, whereas the simulated AUCR is 1.33 using the Applicant's model with the in-house in vitro determined Ki value of 0.3 μM.
2. Based on the clinical observed AUCR of vericiguat with mefenamic acid and the refined Ki value (0.15 μM) of mefenamic acid for UGT1A9, the estimated fmUGT1A9 for vericiguat is 0.52.
3. If assuming the pathways other than glucuronidation accounted for 0.139 of the total clearance of vericiguat, which was estimated based on the mass balance study results, then fmUGT1A1 for vericiguat would be estimated to be 0.34.
4. The Ki value of atazanavir for UGT1A1 was refined to be 0.05 μM to match the observed AUCR of raltegravir with atazanavir which is about 1.7, whereas the simulated AUCR is 1.4 using the Applicant's model with the in-house in vitro determined Ki value of 0.19 μM.
5. Simulate the DDI of vericiguat with atazanavir using the fmUGT1A1 of 0.34 for vericiguat and Ki value of 0.05 μM of atazanavir for UGT1A1. The results are shown in **Table *23***.
6. As indicated in the FDA drug label, mefenamic acid can be taken every 6 hours for up to one week, the reviewer further evaluated the DDI of vericiguat with mefenamic acid using the fmUGT1A9 value of 0.52 for vericiguat and Ki value of 0.15 μM of mefenamic acid for UGT1A9 and a 7-day administration of mefenamic acid. The results are shown in **Table *23***.

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Table 23 Optimized contribution of UGT1A9 and UGT1A1 to the total clearance of vericiguat and Ki value of mefenamic acid and atazanavir mediated inhibitory effect on UGT1A9 and UGT1A1 based on the clinical DDI study results. The DDI of vericiguat with mefenamic acid and atazanavir were re-evaluated with the optimized parameters.

UGT1A9 mediated DDI	Vericiguat model	Mefenamic acid Model			AUCR of vericiguat with mefenamic acid		
		Ki for UGT1A9	Model validation for inhibitory effect of mefenamic acid on dapagliflozin		Observed (3-day admin. of mefenamic acid)	Simulated (3-day admin. of mefenamic acid)	Simulated (7-day admin. of mefenamic acid)
			Observed	Simulated			
Applicant's simulation	fmUGT1A9=0.67 fmUGT1A1=0.19	0.3 μM (in vitro determined)[b]	1 51	1 34[a]	1 20	1 14[a]	1 25
Reviewer's simulation	fmUGT1A9=0.52 fmUGT1A1=0.34	0.15 μM (optimized)	1 51	1 51	1 20	1 20	1 35

UGT1A1 mediated DDI	Vericiguat model	Atazanavir Model			AUCR of vericiguat with atazanavir
		Ki for UGT1A1	Model validation for inhibitory effect of atazanavir on raltegravir		
			Observed	Simulated	
Applicant's simulation	fmUGT1A9=0.67 fmUGT1A1=0.19	0.19 μM (in vitro determined)[b]	Iwamoto 2008: 1.72	1.49[a]	1.12[a]
			Krishna 2016: 1.67	1.43[a]	
			Neely 2010: 1.72	1.44[a]	
Reviewer's simulation	fmUGT1A9=0.52 fmUGT1A1=0.34	0.05 μM (optimized)	Iwamoto 2008: 1.72	1.71[b]	1.27
			Krishna 2016: 1.67	1.71	
			Neely 2010: 1.72	1.73	

Data source: a: Figure 5-12 in PBPK report 20871/PH41143

Applicant's response to FDA's IR

1. In the response to the FDA's IR, the Applicant has completed and submitted the data from in vitro study evaluating the transporters that may be involved in the tubular secretion of M-1 in the kidney and the inhibitory potential of vericiguat and M-1 on those identified transporters.
    a. Uptake of M1 was evaluated in membrane vesicles containing human MRP2 and MRP4. Under the conditions tested, M1 was a substrate of both MRP2 and MRP4.
    b. Vericiguat and M1 did not demonstrate concentration dependent inhibition of MRP2-mediated uptake of [14C] ethacrynic acid-glutathione conjugate (EA-SG) up to the highest concentration tested (100 μM). As such, neither vericiguat nor M-1 are inhibitors of MRP2 at clinically relevant exposures (unbound maximum plasma concentration (Cmax,u) of 18 nM and 44 nM for vericiguat and M-1, respectively following a 10 mg dose.
    c. At the highest concentration tested (100 μM), vericiguat and M1 inhibited MRP4-mediated uptake of [3H] folic acid by 30.6 % and 41.7%, respectively. The estimated IC50 values of vericiguat and M1 for MRP4 were greater than 100 μM. As such, neither vericiguat nor M-1 are inhibitors of MRP4 at clinically relevant exposures.
2. In the response to the FDA's IR, the Applicant provided the assessment results regarding the DDI liability of vericiguat as a victim with a potential UGT1A9 inhibitor by assigning different fmUGT1A9 values in the vericiguat model. Refer to "**Results. 3. Can vericiguat**

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PBPK model predict the effect of mefenamic acid (a UGT1A9 inhibitor) on the PK of vericiguat?" below for the details.

PBPK model application

The developed PBPK model was used to simulate the DDI for vericiguat and M-1 in the following scenarios.

- To predict the effect of mefenamic acid (an UGT1A9 inhibitor) on the PK of vericiguat and M-1 following multiple dose administration of mefenamic acid and a single dose administration of vericiguat in healthy subjects.
- To predict the effect of atazanavir (an UGT1A1 inhibitor) on the PK of vericiguat and M-1 following multiple dose administration of atazanavir and a single dose administration of vericiguat in healthy subjects.

Results

1. Can vericiguat PBPK model describe vericiguat PK in healthy subjects?

Yes. The vericiguat model was able to capture the observed vericiguat PK profiles following a single oral dose administration (0.5, 1, 2.5, 5, 7.5, 10 and 15 mg, Study 15355) or multiple oral dose administration (QD: 1.25, 5, and 10 mg and BID: 5mg, Study 15357) in healthy subjects. (**Table *24*** and **Figure *25***).

2. Can vericiguat and M-1 PBPK model describe M-1 PK in healthy subjects?

An empirical instead of a physiological model was applied to simulate the M-1 plasma PK profiles following a single dose administration (10 mg, Study 17114) and multiple dose administration (10 mg, QD, Study 15357) and urine excretion profile following a single dose administration (10 mg, Study 17114). Although the simulated M-1 PK profiles in plasma and urine matched the observed data well in Study 17114 and Study 15357, the model slightly overpredicted the M1 exposure after a single dose of 5 mg (CmaxR= (b) (4) and AUCR= (b) (4)) in Study 15817 and slightly underpredicted the M1 exposure after a single dose of 2.5 mg (CmaxR= (b) (4) and AUCR= (b) (4)) in Study 17116 (**Table *24*** and **Figure *25***). Given uncertainty in the empirical setting on the M-1 kidney clearance, M-1 model was inadequate when extrapolating to any other clinical scenarios, especially where there are no clinical data available. Refer to "**FDA's assessment**" for the details.

Reference ID: 4722292

Figure 25 Observed and simulated vericiguat and M-1 concentration time profiles following different dosing regimens.

Figure 25.1

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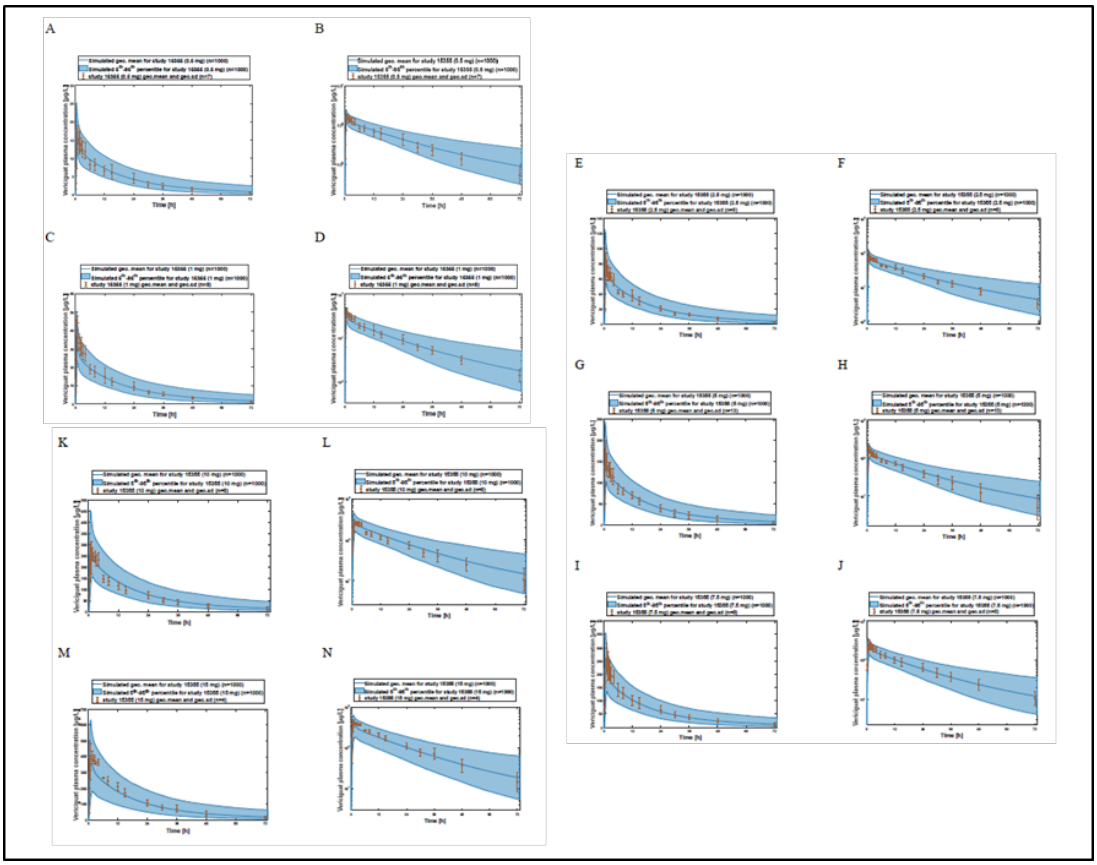

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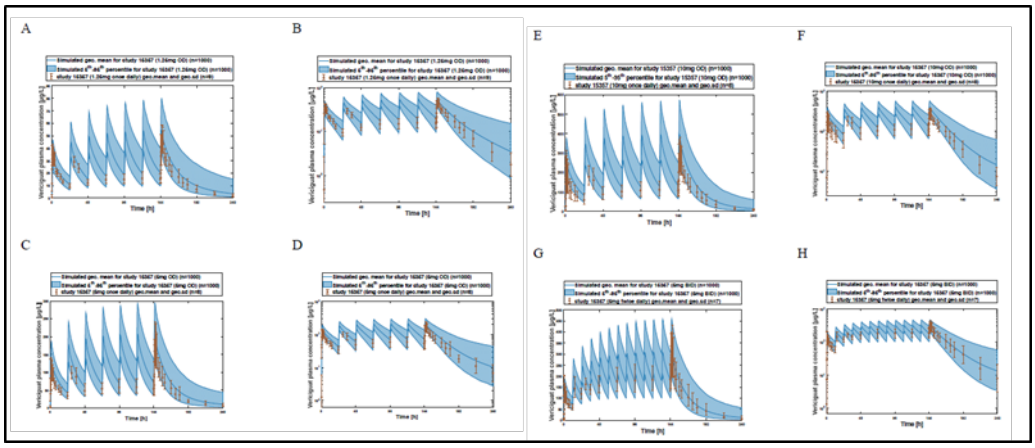
Figure 25.2



(b) (4)

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Figure 25.1 Observed (dots) and simulated (lines) vericiguat plasma concentration-time profiles following a single dose administration in healthy subjects. A and B: 0.5 mg; C and D: 1 mg; E and F: 2.5 mg; G and H: 5mg; I and J: 7.5 mg; K and L: 10 mg; and M and N: 15 mg. A, C, E, G, I, K and M: linear scale and B, D, F, H, J, L and N: logarithmic scale. Observed data were from Study 15355.

Figure 25.2 Observed (dots) and simulated (lines) vericiguat plasma concentration-time profiles following multiple dose administration in healthy subjects. A and B: 1.25 mg QD; C and D: 5 mg QD; E and F: 10 mg QD, and G and H: 5 mg BID. A, C, E, and G: linear scale and B, D, F, and H: logarithmic scale. Observed data were from Study 15357.

(b) (4)

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Table 24 Observed and simulated vericiguat and M-1 geometric mean PK parameters and predicted-to-observed ratios following a single dose or multiple dose administration of vericiguat in healthy subjects.

Study # (arm) - compound	Observed[1,2]		Simulated[2]		predicted-to-observed ratio	
	C_{max} [µg/L]	AUC [µg*h/L]	C_{max} [µg/L]	AUC [µg*h/L]	$C_{max}R$	AUCR
Study 15355, P004 (0.5 mg po) - vericiguat	17.2	273	18.0	331	1.05	1.21
Study 15355, P004 (1 mg po) - vericiguat	39.3	618	36.1	663	0.918	1.07
Study 15355, P004 (2.5 mg po) - vericiguat	82.7	1450	90.1	1650	1.09	1.14
Study 15355, P004 (5 mg po) - vericiguat	158[3]	2900[3]	178[3]	3230[3]	1.13	1.11
Study 15355, P004 (7.5 mg po) - vericiguat	259	4460	257	4660	0.991	1.04
Study 15355, P004 (10 mg po) - vericiguat	285	4940	321	5870	1.13	1.19
Study 15355, P004 (15 mg po) - vericiguat	430	7900	413	7760	0.960	0.982
Study 15817, P012 (5 mg po) - vericiguat	174	3280	157	3030	0.905	0.923
Study 15817, P012 (5 mg po) - M-1	85.7[4]	8180[4]	(b) (4)			
Study 17114, P021 (10 mg po) - vericiguat	255	5750	203	6520	0.796	1.13
Study 17114, P021 (10 mg po) - M-1	272	27700	(b) (4)			
Study 17114, P021 (0.02 mg iv, 30 min infusion) - vericiguat	1.16	12.0	1.06	14.0	0.916	1.17
Study 15357, P006 (1.25 mg po OD, day 1) - vericiguat	38.5	423	35.2	459	0.913	1.08
Study 15357, P006 (5 mg po OD, day 1) - vericiguat	114	1370	141	1810	1.23	1.32
Study 15357, P006 (10 mg po OD, day 1) - vericiguat	200	2240	281	3530	1.40	1.58
Study 15357, P006 (5 mg po BID, day 1) - vericiguat	136	951	141	1140	1.03	1.20
Study 15357, P006 (1.25 mg po OD day 7) - vericiguat	51.4	656	55.3	805	1.08	1.23
Study 15357, P006 (5 mg po OD, day 7) - vericiguat	185	2230	211	2960	1.14	1.33
Study 15357, P006 (10 mg po OD, day 7) - vericiguat	310	3840	409	5590	1.32	1.46
Study 15357, P006 (5 mg po BID, day 7) - vericiguat	312	2600	313	2840	1.00	1.09
Study 15357, P006 (10 mg po OD, day 1) - M-1	223[4]	3370[4]	(b) (4)			
Study 15357, P006 (10 mg po OD, day 7) - M-1	1120[4]	21200[4]				
Study 17116, P023 (2.5 mg po, without mefenamic acid) - vericiguat	75.7	1580	55.1	1440	0.728	0.910
Study 17116, P023 (2.5 mg po, with mefenamic acid) - vericiguat	73.6	1900	58.3	1660	0.792	0.873
Study 17116, P023 (2.5 mg po, without mefenamic acid) - M-1	103	5430[5]	(b) (4)			
Study 17116, P023 (2.5 mg po, with mefenamic acid) - M-1	114	5390[5]				

[1] Source: Observed C_{max} and AUC values are taken from the respective CSRs
[2] C_{max} is the maximum drug concentration after single dose administration or $C_{max,md}$ after multiple dose administration during a dosage interval. AUC is the area under the concentration vs. time curve from zero to infinity after single dose or $AUC_{tau,md}$ during any dosing interval after multiple dose.
[3] Observed values are for non-smokers, whereas simulated values are for non-smokers and smokers
[4] M-1 was measured only exploratively and therefore PK parameters were not reported in the CSR or CTD. (b) (4) (b) (4) Therefore, observed PK parameters were calculated and are reported here for completeness.
[5] AUC was calculated as AUC from time 0 to the last data point >LLOQ.

Data source: Applicant's response to the FDA's information requests (IRs) submitted on September 30, 2020.

3. Can vericiguat PBPK model predict the effect of mefenamic acid (a UGT1A9 inhibitor) on the PK of vericiguat?

Yes. The Applicant has conducted a clinical DDI study (Study17116) of vericiguat with mefenamic acid. A 20% increase in vericiguat exposure was observed when coadministered with mefenamic acid. A three-day dosing regimen of mefenamic acid (500 mg loading dose followed by 250 mg every 6 hours) was used in Study 17116. As indicated in the FDA drug label, mefenamic acid can be taken every 6 hours for up to one week. The reviewer further evaluated the DDI of vericiguat with mefenamic acid and the simulation results showed that one-week administration of mefenamic acid may cause about 30% increase in the exposure of vericiguat. The predicted increase in vericiguat exposure with mefenamic acid is not

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considered clinically relevant given the high variability of vericiguat exposure (33.9%, Table 16, Study 20964, 05D7T5).

In addition, as aforementioned, mefenamic acid is not a strong UGT1A9 inhibitor; results from the DDI of vericiguat with mefenamic acid should not be extrapolated to other UGT1A9 inhibitors without further evaluation. In the response to the FDA's IR, the Applicant provided the assessment results regarding the DDI liability of vericiguat as a victim with a potential UGT1A9 inhibitor by assigning different fmUGT1A9 values in the vericiguat model. As shown in **Table *25***, a strong UGT1A9 inhibitor can cause a 3-fold increase in vericiguat exposure in a situation where UGT1A9 is completed inhibited, while about 2-fold increase in vericiguat exposure was predicted if UGT1A9 activity was inhibited by 50%. Reviewer acknowledges that clinically strong UGT1A9 inhibitors is yet to be identified.

Table 25 Predicted AUCR of vericiguat exposure with and without a potential UGT1A9 inhibitor

Fraction of fmUGT1A9	fmUGT1A9	AUCR
1	0.669	1.00
0.75	0.507	1.52
0.5	0.342	2.04
0	0.00	3.15

4. Can vericiguat PBPK model predict the effect of atazanavir (a UGT1A1 inhibitor) on the PK of vericiguat?

Yes, the Applicant's model predicted AUCR of vericiguat with atazanavir is 1.12. The simulation results using the reviewer's model showed that about 27% increase in vericiguat exposure with atazanavir may occur. Regardless, the predicted increase in vericiguat exposure with atazanavir is not considered clinically relevant given the high variability of vericiguat exposure (33.9%, Table 16, Study 20964, 05D7T5). Refer to "**FDA's assessment**" for the details.

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