CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214377Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Final Report of Sentinel Study

Date: 01/15/2021

Reviewer(s): Yan Li, Ph.D., Division of Epidemiology II
Marie Bradley, Ph.D., Division of Epidemiology II

Division Director: Efe Eworuke, Ph.D., Division of Epidemiology II

Subject: Epidemiology, characteristics, and outcomes of pregnancies in childbearing age women with heart failure

Drug Name(s): Vericiguat (Verquvo)

Application Type/Number: NDA 214377

Applicant/sponsor: Merck

OSE RCM #: 2020-1778

TABLE OF CONTENTS

1 REGULATORY MEMO

To: Theresa Ng, Pharm.D., Risk Management Analyst, Division of Risk Management

From: Yan Li, Ph.D., Epidemiologist, Division of Epidemiology II

Marie Bradley, Ph.D., Team Lead (Acting), Division of Epidemiology II

Through: Efe Eworuke, Ph.D., Deputy Director (Acting), Division of Epidemiology II

Drug Name: Vericiguat (Verquvo)

Subject: Epidemiology, characteristics, and outcomes of pregnancies in childbearing age women with heart failure

Background

In August 2020, the Division of Epidemiology-II (DEPI-II) received a consult request from the Division of Risk Management to estimate the number of childbearing age women with heart failure (HF) and the number of pregnancies among these women, as well as characteristics and outcomes of these pregnancies to support their risk evaluation and mitigation strategy (REMS) review for an ongoing new drug application (NDA #214377) for vericiguat. In response, DEPI-II initiated a study in the FDA's Sentinel System. This memo summarizes findings from the study.

Sentinel study

The full study review is presented in section 2 of this document. In summary, we conducted a retrospective cohort study using data from six large data partners in the FDA's Sentinel System from January 2010 to February 2020. This study has two parts of analyses.

In the first analysis, we estimated the prevalence of childbearing age women with HF and the number of pregnancies among these women in the Sentinel System and used these estimates to project the affected population in the United States in 2019. We identified a total of 144,162 HF cases (prevalence, 0.5%) among 29.5 million eligible women. Within this HF cohort, there were 813 women with 822 pregnancies ending in live birth deliveries (5.5 deliveries per 1,000 women with HF). The prevalence of HF increased monotonically with age from 0.04% in women aged 15-19 years to 1.2% in women aged 50-54 years. The majority of live birth deliveries occurred among young patients, with the 25-29 years groups having the highest proportions (34.7 deliveries per 1,000 women with HF). Across calendar years, the prevalence of HF remained stable (0.3%), as did the rate of deliveries (2.5 to 3.5 deliveries per 1,000 women with HF). Applying the prevalence of HF and HFrEF to the 2019 Census estimates, we projected there were 310,613 women with HF and 85,254 women with HFrEF in the United States in 2019. Among these women, numbers of pregnancies ending in live birth deliveries were 808 and 247, respectively.

In the second analysis, we examined clinical characteristics, HF medication use, and maternal and fetal outcomes of pregnancies in women with HF, and compared them to a

without HF. We identified 489 live birth deliveries (mean age, 32.4) in 487 eligible women with HF. These women had more comorbidities and utilized more health services than pregnant women without HF but were healthier than age-matched non-pregnant HF cases. The baseline mean Charlson/Elixhauser combined comorbidity scores for pregnant women with HF, non-pregnant women with HF, and pregnant women without HF were 2.7, 3.4, and 0.2, respectively. Beta-blockers (21.5%), diuretics (15.3%), and ACE inhibitors (10.2%) were the most commonly used HF medications during the pre-pregnancy period. Utilization of beta-blockers remained unchanged throughout and after pregnancy. Use of ACE inhibitors dropped to 5.3% in the first trimester, to less than 1% in the second and third trimesters but resumed to 8.0% after pregnancy. We observed similar, but less profound decline in the use of diuretics. Use of other HF medications were rare. We observed higher frequencies of cesarean section (35.9% vs 25.3%), preeclampsia (15.0% vs 6.2%), preterm delivery (12.7% vs 5.3%), and peripartum cardiomyopathy (8.8% vs 0.1%) in pregnant women with HF compared to those without HF. Major fetal malformations were identified in mother's claims of 1.6% of pregnancies in women with HF compared to 0.3% in women without HF.

Conclusion

HF is rare among women of childbearing age in the Sentinel System and pregnancies only occurred in a small number of these women. Among women with HF, exposure to embryo-toxic HF medications during pregnancy was rare but did exist. These women had more comorbidities and carried higher risk of adverse maternal and fetal outcomes compared to pregnancies in women without HF.

Recommendation

DEPI was consulted to provide a national estimate for the prevalence of pregnancies among women with HF to assess potential exposure to vericiguat during pregnancy. Based on the low use of HF medications generally, and the specific population (subtype of HF patients (symptomatic chronic HFrEF) vericiguat is indicated for, we expect vericiguat exposure to be limited. Thus, the possibility of inadvertent fetal exposure to vericiguat is likely very low.

2 STUDY REPORT

BACKGROUND

In August 2020, the Division of Epidemiology-II (DEPI-II) received a consult from the Division of Risk Management to estimate the number of childbearing age women with heart failure (HF) and the number of pregnancies among these women, as well as characteristics and outcomes of these pregnancies to support their risk evaluation and mitigation strategy (REMS) review for an ongoing new drug application (NDA #214377) for vericiguat. In response, DPEI-II initiated a study in the Sentinel System.

Vericiguat, a soluble guanylate cyclase (sGC) stimulator, is proposed for the indication of reducing 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 therapies. In animal reproduction studies, oral administration of vericiguat resulted in malformations of heart and major vessels in fetuses, as well as increased number of abortions and resorptions.

The embryo-fetal toxicity seems to be a class effect of sGC stimulators. Riociguat, another drug in this class for treating pulmonary arterial hypertension, is associated with ventricular septal defects and bone malformations in rat studies. As a result, it was approved with a Risk Evaluation and Mitigation Strategy (REMS) to ensure treatment benefits outweigh the risk of embryo-fetal toxicity in females of childbearing age.

In contrast, the REMS Oversight Committee did not recommend a REMS for vericiguat because patients with HF with reduced ejection fraction (HFrEF) are older and more likely to be male, compared to the younger and female predominant pulmonary arterial hypertension population. In addition, several other HF therapies have similar risk of embryo-fetal toxicity but do not have a REMS, including angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), angiotensin receptor-neprilysin inhibitor (ARNI), aldosterone antagonists, and ivabradine.

To further support this regulatory decision, we conducted two analyses in the FDA's Sentinel System. First, we estimated the prevalence of childbearing age women with heart failure (HF) and the number of pregnancies among these women in the Sentinel System, and used these estimates to project the affected population in the United States in 2019. Second, we examined clinical characteristics, HF medication use, and maternal and fetal outcomes of pregnancies in women with HF, and compared them to a cohort of age-matched non-pregnant women with HF, and a cohort of pregnant women without HF.

PART 1: the epidemiology of pregnancy in childbearing age women with HF

METHODS

Data source

This analysis used data from six large data partners (covering more than 90% of the eligible population) in the Sentinel System and the study period ranged from January 2010 to February 2020. The Sentinel System is a national distributed data network of electronic healthcare databases used by the FDA for active surveillance of medical product safety. The data sets contain person-level information on beneficiaries' demographics, diagnoses, and procedures associated with outpatient visits and inpatient stays, and outpatient-filled

prescriptions. As of this query, Sentinel consisted of data on more than 228 million individuals with both medical and drug coverage across the United States with 788 million person-years of observation time.

Study population

As illustrated in **Figure 1**, we included 15- to 54-year-old women with medical and drug insurance coverage for at least 480 days (allowing enrollment gaps of 45 days or less) in the database. This 480-day window covered a 180-day pre-pregnancy period and a pregnancy episode up to 300 days.

Pregnancies ending in live birth deliveries were identified using a validated algorithm based on International Classification of Diseases, 9th or 10th Revision, Clinical Modification (ICD-9/10-CM) diagnosis and procedure codes.[1] The date of delivery was set as the index date (i.e., Day 0). We excluded women with a prior recorded live birth or stillbirth delivery in the 301 days before the index date. To identify women with established HF before pregnancy, we required qualifying HF diagnoses during the 180-day pre-pregnancy period or first trimester, defined as (1) one HF diagnosis in the inpatient care setting during the [-480 to -180] day window prior to index date; (2) two HF diagnosis in the outpatient care setting during the [-480 to -1] day window prior to index date, one of which had to occur before day -180; or (3) one HF diagnosis in the outpatient care setting during the [-480 to -180] day window prior to index date and an oral HF-related medication dispensed within 60 days of that diagnosis. The 180-day cut-off, which approximated the end of the first trimester, was used to identify patients with pre-existing HF, because new-onset HF in pregnant women rarely occurred during the first trimester.[2]

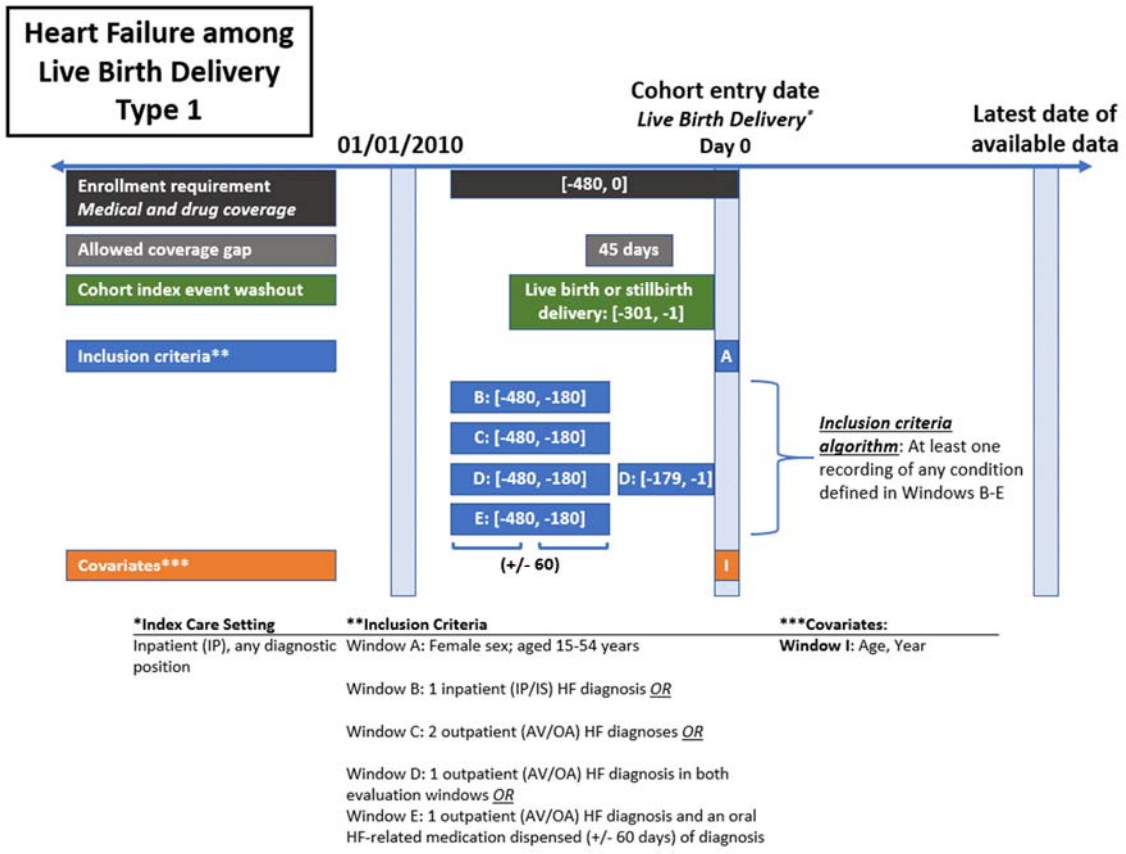


Figure 1. Illustration of the study design

To understand the background rate of pregnancy, we identified all childbearing age women with qualifying HF diagnoses in the database (regardless of pregnancy status). In that analysis, the requirement for live birth deliveries was removed.

Statistical analysis

The prevalence of HF was equal to the number of women with HF divided by the number of eligible women in the database. We also calculated the number of live birth deliveries per 1,000 women with HF. In a subgroup analysis, we stratified results by age and calendar year, in which a woman can contribute to more than one subgroup.

We conducted two sensitivity analyses. First, we restricted the study population to HF with reduced ejection fraction (HFrEF). Second, we included not only pregnancies ending in live birth deliveries but also pregnancies ending in stillbirth deliveries.

To project the total of number of women with HF in the United States in 2019, we multiplied age-stratified estimates obtained in this study by the number of women in the corresponding age categories of the 2019 Census estimates.[a] We then multiplied the estimated number of women with HF by the pregnancy rate in 2019 to project the number of pregnancies.

RESULTS

Estimates in the Sentinel system

Among 29.6 million women of child-bearing age in the database, we identified a total of 144,162 HF cases (prevalence, 0.5%). Within this HF cohort, there were 813 women with 822 pregnancies ending in live birth deliveries (5.7 live birth deliveries per 1,000 women with HF). Using an algorithm specifically for HFrEF, we identified 39,844 women (prevalence, 0.1%). Among them, there were 221 women with 223 pregnancies ending in live birth deliveries (5.5 live birth deliveries per 1,000 women with HFrEF).

As shown in **Table 1**, the prevalence of HF increased monotonically with age which reached 1.2% in the 50-54 years group. The majority of live birth deliveries occurred among younger patients, with the 25-29 years group having the highest proportion (34.7 live birth deliveries per 1,000 women with HF). Across the study period, the prevalence of HF remained stable (0.3%), as did the rate of deliveries (2.6 to 3.6 live birth deliveries per 1,000 women with HF). Including stillbirth deliveries barely changed the observed trends.

Table 1. Live Birth or Stillbirth Deliveries among Women with Heart Failure (HF) in the Sentinel Distributed Database between January 1, 2010 and February 29, 2020

	# of eligible women in the database	# of women with HF	Prevalence of HF, %	# of live birth deliveries among women with HF	# of live birth deliveries per 1,000 women with HF	# of live birth or stillbirth deliveries among women with HF	# of live birth or stillbirth deliveries per 1,000 women with HF
Total	29,535,188	144,162	0.5%	822	5.7	846	5.8
Age group							
15-19	4,651,623	1,735	0.04%	11	6.3	11	6.3

[a] Annual Estimates of the Resident Population for Selected Age Groups by Sex for the United States: April 1, 2010 to July 1, 2019. https://www2.census.gov/programs-surveys/popest/tables/2010-2019/national/asrh/nc-est2019-agesex.xlsx. Accessed on Oct 1, 2020.

20-24	5,033,406	3,133	0.06%	81	25.5	84	26.5
25-29	5,673,276	4,932	0.09%	171	34.7	172	34.9
30-34	5,514,271	9,177	0.2%	247	26.8	255	27.6
35-39	5,477,578	14,853	0.3%	211	14.1	215	14.4
40-44	5,518,878	24,418	0.4%	65	2.6	68	2.7
45-49	5,780,940	42,013	0.7%	21	0.5	22	0.5
50-54	5,885,323	69,710	1.2%	15	0.2	19	0.3
Year							
2010	9,417,397	28,772	0.3%	84	2.9	87	3.0
2011	8,951,714	26,969	0.3%	94	3.5	96	3.6
2012	8,647,256	25,475	0.3%	78	3.1	79	3.1
2013	8,546,556	24,680	0.3%	72	2.9	73	3.0
2014	9,189,860	26,571	0.3%	83	3.1	86	3.2
2015	9,667,980	29,132	0.3%	88	3.0	92	3.2
2016	9,899,429	31,321	0.3%	91	2.9	96	3.1
2017	10,133,960	31,827	0.3%	84	2.6	84	2.6
2018	9,658,004	28,371	0.3%	72	2.5	74	2.6
2019	9,248,525	27,637	0.3%	72	2.6	75	2.7
2020[1]	3,875,117	8,116	0.2%	4	0.5	4	0.5

[1] The 2020 data ended in February, resulting in irregularly small counts

As shown in **Table 2**, the prevalence of HFrEF also increased monotonically with age, from 0.015% in the 15-19 years group to 0.3% in the 50-54 years group. The majority of live birth deliveries occurred among younger patients, with the 25-29 years group having the highest proportion (33.6 live birth deliveries per 1,000 women with HFrEF). Across the study period, the prevalence of HF remained stable (0.1%). The rate of deliveries ranged from 1.8 to 3.5 live birth deliveries per 1,000 women with HFrEF). Including stillbirth deliveries barely changed our estimates.

Table 2. Live Birth or Stillbirth Deliveries among Women with Heart Failure with Reduced Ejection Fraction (HFrEF) in the Sentinel Distributed Database between January 1, 2010 and February 29, 2020

	# of eligible women in the database	# of women with HFrEF	Prevalence of HFrEF, %	# of live birth deliveries among women with HFrEF	# of live birth deliveries per 1,000 women with HFrEF	# of live birth or stillbirth deliveries among women with HFrEF	# of live birth or stillbirth deliveries per 1,000 women with HFrEF
Total	29,535,188	39,844	0.1%	218	5.4	223	5.5
Age group							
15-19	4,651,623	416	0.01%	1	2.4	1	2.4
20-24	5,033,406	922	0.02%	24	26.0	25	27.1
25-29	5,673,276	1,520	0.03%	51	33.6	51	33.6
30-34	5,514,271	2,781	0.1%	59	21.2	62	22.3
35-39	5,477,578	4,317	0.1%	56	13.0	57	13.2
40-44	5,518,878	6,800	0.1%	14	1.9	14	1.9
45-49	5,780,940	11,350	0.2%	8	0.7	8	0.7
50-54	5,885,323	18,459	0.3%	5	0.3	5	0.3
Year							
2010	9,417,397	6,408	0.1%	21	3.3	21	3.3
2011	8,951,714	6,248	0.1%	22	3.5	22	3.5
2012	8,647,256	5,909	0.1%	17	2.9	17	2.9
2013	8,546,556	5,755	0.1%	20	3.5	20	3.5

2014	9,189,860	6,112	0.1%	18	2.9	19	3.1
2015	9,667,980	6,743	0.1%	12	1.8	13	1.9
2016	9,899,429	8,631	0.1%	23	2.7	25	2.9
2017	10,133,960	10,116	0.1%	31	3.1	31	3.1
2018	9,658,004	9,296	0.1%	24	2.6	25	2.7
2019	9,248,525	9,350	0.1%	27	2.9	27	2.9
2020[1]	3,875,117	2,789	0.1%	3	1.1	3	1.1

[1] The 2020 data ended in February, resulting in irregularly small counts

Population projections based on the Census data

Applying the prevalence of HF and HFrEF to the 2019 Census estimates (**Table 3**), we projected there were 310,613 women with HF and 85,254 women with HFrEF in the United States in 2019. Among these women, numbers of pregnancies ending in live birth deliveries were 808 and 247, respectively.

Table 3. Projected numbers of women with heart failure (HF) and heart failure with reduced ejection fraction (HFrEF) in the United States in 2019

Age group	# of women in the United States (2019 census estimates)	Prevalence of HF in our study	Estimated # of women with HF	Prevalence of HFrEF in our study	Estimated # of women with HFrEF
15-19	10,308,963	0.04%	3845	0.01%	922
20-24	10,568,188	0.06%	6578	0.02%	1936
25-29	11,504,446	0.09%	10001	0.03%	3082
30-34	11,076,695	0.2%	18434	0.1%	5586
35-39	10,852,580	0.3%	29428	0.1%	8553
40-44	10,014,484	0.4%	44309	0.1%	12339
45-49	10,312,396	0.7%	74945	0.2%	20247
50-54	10,390,540	1.2%	123073	0.3%	32589
Total # of women with HF or HFrEF in 2019			310613		85254
# of live birth deliveries per 1,000 women with HF or HFrEF in 2019 in table 2			2.6		2.9
# of live birth deliveries			808		247

PART 2: characteristics and outcomes of pregnancies in women with HF

METHODS

Data source

This analysis used data from four large data partners in the Sentinel System, in which a Mother Infant Linkage (MIL) table was available. The study period ranged from January 2010 to February 2020.

Study population

As illustrated in **Figure 2**, we included 15- to 54-year-old women with medical and drug insurance coverage for at least 574 days (allowing enrollment gaps of 45 days or less) in the database. This 574-day window covered a 183-day pre-pregnancy period, a pregnancy episode up to 301 days, and a 90-day post-pregnancy period.

Pregnancies ending in live birth deliveries were identified using a validated algorithm based on International Classification of Diseases, 9th or 10th Revision, Clinical Modification (ICD-9/10-CM) diagnosis and procedure codes.[1] The date of delivery was set as the index date

(i.e., Day 0). We restricted the study sample to deliveries linked to an infant record per the Sentinel MIL Table. To identify women with preexisting HF before pregnancy, we imposed one of the following inclusion criteria: (1) one HF diagnosis in the inpatient care setting during the [-480 to -180] day window prior to index date; (2) two HF diagnosis in the outpatient care setting during the [-480 to -1] day window prior to index date, one of which had to occur before day -180; or (3) one HF diagnosis in the outpatient care setting during the [-480 to -180] day window prior to index date and an oral HF-related medication dispensed within 60 days of that diagnosis. The 180-day cut-off, which approximated the end of first trimester, was used to identify patients with pre-existing HF, because new-onset HF in pregnant women rarely occurred during the first trimester.[2] Pregnant women who didn't meet the above criteria for HF were included in the non-HF pregnant cohort.

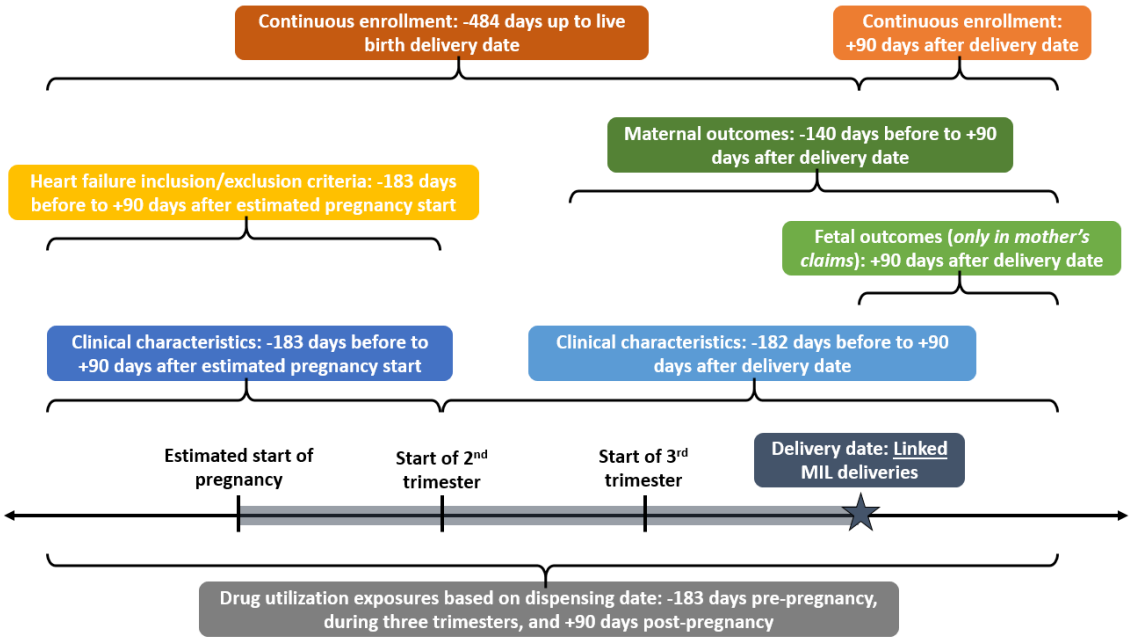


Figure 2. Illustration of the study design

For each pregnancy episode identified in the pregnant HF cohort, an age-matched non-pregnant comparator episode was selected from eligible women within the same data partner who also met the HF inclusion criteria and whose enrollment time overlaps with the enrollment time of pregnant women with HF. We assembled three cohorts of interest: pregnant women with HF, age-matched non-pregnant women with HF, and pregnant women without HF.

Statistical analysis

We examined demographic and clinical characteristics, changes in HF medication use, and maternal and infant outcomes (for pregnant cohort only) across three cohorts of interest.

Demographic and clinical characteristics were assessed during the 183-day pre-pregnancy period and the first trimester, which included age, alcohol abuse, cardiac arrhythmia, cardiac valvular disease, cardiomyopathy, chronic kidney disease, congenital heart disease, pre-existing diabetes, drug abuse, preexisting hypertension, ischemic heart disease, overweight or obesity, pulmonary hypertension, rheumatic heart disease, thyroid disease, tobacco use, Charlson/Elixhauser combined comorbidity score, mean number of ambulatory encounters, mean number of emergency room encounters, mean number of

inpatient hospital encounters, mean number of unique drug classes dispensed, and mean number of unique dispensings. Gestational diabetes and gestational hypertension were assessed during the second or third trimester.

Use of HF medications was assessed separately during the 183-day pre-pregnancy period, the first trimester, the second trimester, the third trimester, and the 90-day post-pregnancy period, which included angiotensin-converting-enzyme (ACE) inhibitors, aldosterone antagonists, Angiotensin II receptor blockers (ARBs), angiotensin receptor neprilysin inhibitor (ARNI), beta blockers, digoxin, diuretics, hydralazine and nitrates, and ivabradine.

For the non-pregnant HF cohort, these variables were assessed during the corresponding matched time window.

Most maternal and infant outcomes were assessed on the date of or up to 90 days after delivery using the mother's claims, which included postpartum hemorrhage, preterm delivery, multiple gestation, cesarean section, small for gestational age, congenital cardiac malformation, bone or skeletal malformation, other major congenital malformation, and any major malformation. Preeclampsia was evaluated in the second and third trimesters and 30 days after the delivery. Peripartum cardiomyopathy was evaluated in the second and third trimesters and 90 days after the delivery.

In a sensitivity analysis, we restricted the study population to patients with HFrEF.

RESULTS

Demographic and clinical characteristics

We identified 489 pregnancies (mean age, 32.4) in the pregnant HF cohort and 489 age-matched episodes (mean age, 32.4) in the non-pregnant HF cohort. We also identified 1,245,931 pregnancies (mean age, 31.6) in the non-HF pregnancy cohort. Baseline demographic and clinical characteristics of these individuals are shown in **Table 4**.

Women with HF (regardless of pregnancy status) had more comorbidities and utilized more health services compared with women without HF. Many of them had underlying heart diseases, such as cardiac arrhythmia, cardiac valvular disease, and cardiomyopathy. Risk factors for cardiovascular diseases were also prevalent, especially hypertension and overweight or obesity. Comparing the two HF cohorts, women who became pregnant were relatively healthier than matched non-pregnant women with HF. The mean Charlson/Elixhauser combined comorbidity scores for pregnant women with HF, non-pregnant women with HF, and pregnant women without HF were 2.7, 3.4, and 0.2, respectively.

Table 4. Demographic and clinical characteristics of pregnant women with heart failure (HF), non-pregnant women with HF, and pregnant women without HF in the Sentinel Distributed Database between January 1, 2010 and February 29, 2020

Characteristic	Pregnant women with HF		Non-pregnant women with HF		Pregnant women without HF	
	N/Mean	%/SD[1]	N/Mean	%/SD[1]	N/Mean	%/SD[1]
# of unique women	487	--	477	--	1,076,117	--
# of pregnancies	489	--	489	--	1,245,931	--
Mean Age	32.4	5.0	32.4	5.0	31.6	4.5
15-19	5	1.0%	5	1.0%	25,692	2.1%

20-24	36	7.4%	36	7.4%	91,625	7.4%
25-29	116	23.7%	116	23.7%	326,764	26.2%
30-34	177	36.2%	177	36.2%	497,006	39.9%
35-39	120	24.5%	120	24.5%	251,361	20.2%
40-44	31	6.3%	31	6.3%	50,085	4.0%
Age: 45-49	3	0.6%	3	0.6%	3,122	0.3%
Age: 50-54	1	0.2%	1	0.2%	276	0.0%
Comorbidities						
Alcohol abuse	4	0.8%	9	1.8%	2,784	0.3%
Cardiac arrhythmia	111	22.8%	144	29.4%	10,579	1.0%
Cardiac valvular disease	117	24.0%	134	27.4%	6,413	0.6%
Cardiomyopathy	106	21.8%	159	32.5%	490	0.0%
Chronic kidney disease	15	3.1%	57	11.7%	2,610	0.2%
Congenital heart disease	64	13.1%	50	10.2%	3,460	0.3%
Diabetes (preexisting)	60	12.3%	104	21.3%	16,111	1.5%
Drug abuse	13	2.7%	41	8.4%	8,714	0.8%
Hypertension (preexisting)	207	42.5%	282	57.7%	33,458	3.1%
Ischemic heart disease	45	9.2%	71	14.5%	1,233	0.1%
Overweight or obesity	119	24.4%	148	30.3%	53,570	5.0%
Pulmonary hypertension	20	4.1%	27	5.5%	209	0.0%
Rheumatic heart disease	36	7.4%	40	8.2%	1,377	0.1%
Thyroid disease	101	20.7%	96	19.6%	90,661	8.4%
Tobacco use	63	12.9%	84	17.2%	43,091	4.0%
Gestational diabetes	99	20.3%	2	0.4%	170,064	15.8%
Gestational hypertension	82	16.8%	7	1.4%	103,865	9.7%
Charlson/Elixhauser combined comorbidity score	2.7	1.4	3.4	2.1	0.2	0.5
Health service utilization						
# of ambulatory encounters	16.4	14.8	20.4	30.2	8.4	8.2
# of emergency room encounters	1.2	1.9	1.7	2.9	0.3	0.9
# of inpatient hospital encounters	0.5	0.9	0.8	1.5	0.0	0.2
# of unique drug classes dispensed	6.5	4.3	8.2	5.5	3.1	3.0
# of unique dispensings	15.1	14.5	25.7	23.6	6.0	7.4

[1]In the pregnant cohorts, baseline characteristics and health service utilization intensity were assessed using denominators of the total number of unique women in each cohort since only the first pregnancy episode per total unique women was selected. For the non-pregnant cohort, the total number of matched non-pregnant comparator episodes was used as the denominator.

Table 5. Heart failure (HF) medication use before, during, and after pregnancy (or corresponding matched time window for the non-pregnant women)

HF medications	Any use in the pre-pregnancy period		Any use in the first trimester		Any use in the second trimester		Any use in the third trimester		Any use in the post-pregnancy period[1]	
	N	%	N	%	N	%	N	%	N	%
Pregnant women with HF (N = 489 pregnancies per 487 total unique women)										
ACE inhibitors[2]	50	10.2%	26	5.3%	5	1.0%	2	0.4%	39	8.0%
Aldosterone antagonists	18	3.7%	8	1.6%	3	0.6%	2	0.4%	9	1.8%
ARBs[2]	18	3.7%	9	1.8%	2	0.4%	2	0.4%	14	2.9%
ARNI[2]	1	0.2%	2	0.4%	0	0.0%	0	0.0%	2	0.4%
Beta blockers	105	21.5%	107	21.9%	95	19.4%	98	20.0%	115	23.6%
Digoxin	6	1.2%	8	1.6%	8	1.6%	8	1.6%	10	2.1%
Diuretics	75	15.3%	47	9.6%	22	4.5%	29	5.9%	71	14.6%
Hydralazine and nitrates	11	2.2%	7	1.4%	8	1.6%	7	1.4%	13	2.7%
Ivabradine	2	0.4%	1	0.2%	0	0.0%	0	0.0%	0	0.0%
Non-pregnant women with HF										
ACE inhibitors[2]	108	22.1%	107	21.9%	104	21.3%	92	18.8%	106	21.7%
Aldosterone antagonists	47	9.6%	57	11.7%	54	11.0%	53	10.8%	55	11.2%
ARBs[2]	46	9.4%	41	8.4%	39	8.0%	43	8.8%	41	8.4%
ARNI[2]	2	0.4%	3	0.6%	2	0.4%	2	0.4%	3	0.6%
Beta blockers	163	33.3%	185	37.8%	179	36.6%	172	352%	184	37.6%
Digoxin	22	4.5%	19	3.9%	15	3.1%	16	3.3%	19	3.9%
Diuretics	131	26.8%	135	27.6%	128	26.2%	126	25.8%	133	27.2%
Hydralazine and nitrates	18	3.7%	22	4.5%	25	5.1%	23	4.7%	22	4.5%
Ivabradine	2	0.4%	1	0.2%	2	0.4%	3	0.6%	1	0.2%
Pregnant women without HF (N = 1,246,489 pregnancies per 1,076,561 total unique women)										
ACE inhibitors[2]	3,677	0.3%	2,399	0.2%	321	0.0%	151	0.0%	4,221	0.4%

Aldosterone antagonists	2,565	0.2%	1,008	0.1%	86	0.0%	51	0.0%	1,106	0.1%
ARBs[2]	1,444	0.1%	938	0.1%	85	0.0%	48	0.0%	1,079	0.1%
ARNI[2]	0	0.0%	0	0.0%	0	0.0%	0	0.0%	18	0.0%
Beta blockers	12,975	1.0%	14,933	1.2%	15,844	1.3%	21,677	1.7%	37,008	3.4%
Digoxin	42	0.0%	40	0.0%	62	0.0%	157	0.0%	129	0.0%
Diuretics	7,106	0.6%	4,772	0.4%	993	0.1%	905	0.1%	14,391	1.3%
Hydralazine and nitrates	122	0.0%	171	0.0%	127	0.0%	205	0.0%	993	0.1%
Ivabradine	1	0.0%	1	0.0%	0	0.0%	0	0.0%	2	0.0%

[1] Due to the limitation of Sentinel routine query tool, the denominator for the post-pregnancy evaluation was the total number of unique women rather than pregnancies (N = 487 and 1,076,117 for pregnant women with and without HF, respectively).

[2] ACE: angiotensin-converting-enzyme; ARBs: Angiotensin II receptor blockers; ARNI: angiotensin receptor neprilysin inhibitor

As shown in **Table 5**, beta-blockers (21.5%), diuretics (15.3%) and ACE inhibitors (10.2%) were the most commonly used HF medications during the pre-pregnancy period. Use of other HF medications was limited. Utilization rates of beta-blockers remained unchanged throughout and after pregnancy. Use of ACE inhibitors dropped to 5.3% in the first trimester, to less than 1% in the second and third trimesters, but resumed to 8.0% after pregnancy. We observed similar, but less profound decline in the use of diuretics. In contrast, utilization rates of HF medications were stable during the corresponding matched time window for non-pregnant women with HF.

In pregnant women without HF, about 1% of individuals used beta-blockers during the pre-pregnancy period, which gradually increased to 3.4% during the post-pregnancy period. Utilization of other HF medications was very low, especially during the second and third trimesters.

Table 6 shows maternal and fetal outcomes of pregnant women with and without HF. We observed higher frequencies of cesarean section (35.9% vs 25.3%), preeclampsia (15.0% vs 6.2%), and preterm delivery (12.7% vs 5.3%) in pregnant women with HF compared to those without HF. Notably, 8.8% of pregnant women with HF developed peripartum cardiomyopathy, compared with 0.1% in pregnant women without HF. Major fetal malformations were identified in mother's claims of 1.6% of pregnancies in women with HF compared to 0.3% in women without HF, which was mostly contributed by major cardiac malformations (1.4% vs 0.1%)

Table 6. Maternal and fetal outcomes of pregnancies among women with and without heart failure (HF)

	Pregnancies among women with HF (N = 497 pregnancies)		**Pregnancies among women without HF (N = 1,076,117 pregnancies)**	
	N	%	N	%
Maternal outcomes				
Preeclampsia	73	15.0%	66,966	6.2%
Mild or unspecified preeclampsia	68	14.0%	55,604	5.2%
Severe preeclampsia / eclampsia	22	4.5%	25,049	2.3%
Peripartum cardiomyopathy	43	8.8%	1,041	0.1%
Postpartum hemorrhage	22	4.5%	33,236	3.1%
Preterm delivery	62	12.7%	56,504	5.3%
Multiple gestation	1	0.2%	934	0.1%
Cesarean section	175	35.9%	272,625	25.3%
Infant outcomes				
Small for gestational age	8	1.6%	18,998	1.8%
Congenital cardiac malformation	7	1.4%	726	0.1%
Ventricular septal defect	0	0.0%	7	0.0%
Right ventricular outflow tract obstruction	0	0.0%	1	0.0%
Other cardiac malformation	7	1.4%	721	0.1%
Bone or skeletal malformation	0	0.0%	863	0.1%

Other major congenital malformation	1	0.2%	1,367	0.1%
Any major malformation	8	1.6%	2,878	0.3%

In the sensitivity analysis among those with HFrEF, we only identified 91 pregnancies in women with HFrEF and 87 matched non-pregnant episodes in women with HFrEF (**Appendix section 3.3 Tables 4, 5, and 6**). Underlying heart diseases were more prevalent in this subset, as well as the use of HF medications, but frequencies of adverse maternal and fetal outcomes were similar to patients with HF.

DISCUSSION

With increases in blood volume and cardiac output, pregnancy poses a significant risk of morbidity and mortality to women with underlying heart diseases.[3,4] In this large sample of women of childbearing age, we found pregnancies ending in live birth or stillbirth deliveries were rare among those with HF. We examined characteristics and outcomes of these pregnancies and compared them with pregnancies in women without HF. We found among childbearing age women with HF, exposure to embryo-toxic HF medications during pregnancy was rare but did exist. These women had more comorbidities and carried higher risk of adverse maternal and fetal outcomes compared to pregnancies in women without HF

HF is relatively rare among women of childbearing age. Using data from the National Health and Nutrition Examination Survey from 2013 to 2016, a study found the prevalence of HF is 0.2% and 1.7% among women 20 to 39 and 40 to 59 years of age, respectively.[5] The estimates from our study in the Sentinel System using administrative claims data were comparable to estimates in this survey-based study. In our analysis, HFrEF only accounted for about 28% of all HF cases, compared to 45% in studies based on echocardiographic imaging data.[6,7] This underestimation is expected given the unavailability of ejection fraction measurements in claims databases and the fact that more than 40% of diagnostic codes for HF in claims were nonspecific.[8]

To our knowledge, this is the first study that examined the rate of pregnancy among women with established HF. Available data concerning HF and pregnancy have mostly focused on HF related encounters during peripartum and postpartum periods. An analysis of the Nationwide Inpatient Sample suggested HF diagnoses existed in about 0.1% of all pregnancy related hospitalizations in the United States from 2001 to 2011.[9] A large proportion of these diagnoses represented new-onset HF (e.g., HF associated with peripartum cardiomyopathy) and occurred during the postpartum period. Without information on patients' medical history, it is not clear whether and how often women with established HF become pregnant. Our study fills this knowledge gap by capturing HF diagnoses before pregnancy, or during the first trimester in which such diagnoses likely suggest pre-existing conditions.

Vericiguat is indicated in patients with symptomatic chronic HFrEF who recently experience HF worsening events (HF hospitalization or need of outpatient intravenous diuretics), which only represent a small proportion of the total HF population. The feasibility assessment provided by the sponsor suggests about 1 in 3 patients with HFrEF had a recent HF worsening event and would be indicated for vericiguat.[b] Assuming every one of these women receives vericiguat, we would expect 82 vericiguat exposed

[b] Bayer. Response to FDA on Mid-cycle meeting – Safety/PV comment. \\CDSESUB1\evsprod\nda214377\0023\m1\us\multi-module-info-amendment-18sep2020.pdf

pregnancies (247/3 ≈ 82) in the United States in 2019. The feasibility assessment also indicates the peak forecast for vericiguat use in the worsening HF population is 12%. If that is the case, we would only expect 10 vericiguat exposed pregnancies (247*0.12/3 ≈ 10) in the United States in 2019. To summarize, based on data in 2019, the number of vericiguat exposed pregnancies in the United States is expected to range from 10 to 82.

For women with cardiac disease who have pregnancy intention, proper pre-conception counselling, evaluation, and risk stratification are essential to optimize patient outcomes. In some women, pregnancy might pose prohibitive maternal risk.[10] We found women with HF who had live birth deliveries had fewer comorbidities than their non-pregnant counterparts, likely because pregnancies are intentionally avoided in more severe HF patients or because pregnancies in patients with more severe conditions are terminated early either spontaneously or therapeutically.

Modifying existing HF medications to avoid fetal harm is an important aspect of pre-pregnancy management for patients with HF because many of these medications are teratogenic, including ACE inhibitors, ARBs, ARNI, ivabradine, and aldosterone antagonists.[10,11] We found such cases were rare but did exist in our sample, indicating room for quality improvement in patient management and emphasizing the need for continuous patient monitoring.

In our study, pregnancies in women with HF not only had higher frequencies of adverse maternal outcomes as expected, but also higher frequencies of major fetal malformations, especially major cardiac malformations. This excessive risk of major cardiac malformations might be attributed to multiple non-inherited and inherited risk factors. In addition to higher frequency of potentially teratogenic HF medication use, we observed higher prevalence of diagnoses for drug/alcohol abuse, tobacco use, and congenital heart disease in women with HF than women without HF. However, our study sample is too small of fully elucidate the potential association.

This study is subject to several other limitations. First, despite its large sample size, the Sentinel System primarily comprises individuals with private health insurance. Therefore, the study findings may not be generalizable to publicly insured women (i.e., those covered by Medicaid). Second, our study only captured pregnancies ending in live birth or stillbirth deliveries and missed those ending in spontaneous or therapeutic abortions. As a result, we likely underestimated the overall pregnancy rate. However, the degree of underestimation might be small. According to a large registry involving 2,032 pregnancies in women with heart diseases, only 4% of pregnancies (82 pregnancies) ended in spontaneous or therapeutic abortions.[2] Third, we relied on diagnostic codes in claims data to identify patients with HF, which may lead to misclassification, especially for outpatient encounters. To overcome this, we required additional data elements (additional visit or HF medication dispensing) for outpatient encounters to increase the specificity of the definition.[12] Forth, prescription claims only reflect the dispensed medications, so we cannot determine whether medications are actually taken by patients. On the contrary, studies relying on patient's self-report would suffer from recall bias. Lastly, due to the limitation of Sentinel's routine querying tools, we only ascertained fetal outcomes using mother's claims. This likely rendered underestimated results. Additional queries using infant's claims are needed for more complete assessment.

CONCLUSION

HF is rare among women of childbearing age in the Sentinel System and pregnancies only occurred in a small number of these women. Among women with HF, exposure to potentially embryo-toxic HF medications during pregnancy was rare but did exist. These women had more comorbidities and carried higher risk of adverse maternal and fetal outcomes compared to pregnancies in women without HF. Vericiguat exposure is expected to be limited to a small proportion of a specific subtype of HF patients (symptomatic chronic HFrEF) in the United States. Therefore, the possibility of inadvertent fetal exposure to vericiguat is likely very low.

REFERENCES

1. Li Q, Andrade SE, Cooper WO, et al. Validation of an algorithm to estimate gestational age in electronic health plan databases. *Pharmacoepidemiology and drug safety.* 2013;22(5):524-532.
2. Silversides CK, Grewal J, Mason J, et al. Pregnancy Outcomes in Women With Heart Disease: The CARPREG II Study. *J Am Coll Cardiol.* 2018;71(21):2419-2430.
3. European Society of G, Association for European Paediatric C, German Society for Gender M, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J.* 2011;32(24):3147-3197.
4. Ruys TP, Roos-Hesselink JW, Hall R, et al. Heart failure in pregnant women with cardiac disease: data from the ROPAC. *Heart.* 2014;100(3):231-238.
5. Virani SS, Alonso A, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation.* 2020;141(9):e139-e596.
6. Bursi F, Weston SA, Redfield MM, et al. Systolic and diastolic heart failure in the community. *JAMA.* 2006;296(18):2209-2216.
7. Shah KS, Xu H, Matsouaka RA, et al. Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. *J Am Coll Cardiol.* 2017;70(20):2476-2486.
8. Masri A, Althouse AD, McKibben J, Lee JS, Mulukutla SR. Limitations of Administrative Data for Studying Patients Hospitalized With Heart Failure. *Ann Intern Med.* 2017;166(12):916-917.
9. Mogos MF, Piano MR, McFarlin BL, Salemi JL, Liese KL, Briller JE. Heart Failure in Pregnant Women: A Concern Across the Pregnancy Continuum. *Circ Heart Fail.* 2018;11(1):e004005.
10. Stergiopoulos K, Shiang E, Bench T. Pregnancy in patients with pre-existing cardiomyopathies. *J Am Coll Cardiol.* 2011;58(4):337-350.
11. 2018 ESC Guidelines for themanagement of cardiovascular diseases during pregnancy. *Rev Esp Cardiol (Engl Ed).* 2019;72(2):161.
12. Saczynski JS, Andrade SE, Harrold LR, et al. A systematic review of validated methods for identifying heart failure using administrative data. *Pharmacoepidemiology and drug safety.* 2012;21 Suppl 1:129-140.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YAN LI
01/15/2021 05:28:33 PM

MARIE N BRADLEY
01/15/2021 05:31:29 PM

EFE EWORUKE
01/15/2021 05:32:38 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 14, 2021
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214377
Product Name and Strength:	Verquvo (vericiguat) tablets, 2.5 mg, 5 mg and 10 mg
Applicant/Sponsor Name:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
OSE RCM #:	2020-1052-3
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on January 13, 2021 for Verquvo. We reviewed the revised container labels for Verquvo (Appendix A) to determine if it is acceptable from a medication error perspective. The applicant made changes to the language of the Medication Guide and updated the container labels to reflect these changes on the "Peel Away" portion.

2 CONCLUSION

We find the proposed container labels acceptable from a medication error perspective and we have no additional recommendations at this time.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MAXIMILIAN STRAKA
01/14/2021 11:52:39 AM

HINA S MEHTA
01/14/2021 01:02:07 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: January 7, 2021

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst
DCN

To: Alexis Childers
DCN

Subject: QT Consult to NDA 214377 (SDN 034)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 11/18/2020 regarding the nonclinical study reports. We reviewed the following materials:

- Sponsor's summary of nonclinical findings (NDA 214377 / eCTD 0033; link);
- Nonclinical study report TT209425FIN evaluating effect of BAY1021189 and BAY1222707 on hERG, Peak Nav 1.5 and KvLQT1/minK (NDA 214377 / eCTD 0033; link);
- Nonclinical study report TT204803FIN evaluating effect of BAY1021189 and BAY1222707 on KvLQT1/minK (NDA 214377 / eCTD 0033; link); and
- Nonclinical raw datasets for TT209425FIN and TT204803FIN (NDA 214377 / eCTD 0036; link); and
- Previous IRT reviews for NDA 214377 dated 08/25/2020 and 11/04/2020 in DARRTS.

1 Responses for the Division

We have reviewed the raw data and reports for the additional nonclinical experiments conducted. Our review of the information is consistent with the sponsor's conclusions and we have not observed significant changes in IC_{50} values. The nonclinical data, therefore, supports the conclusion that it is unlikely that direct ion channel interaction (with any of the major cardiac ionic currents) explains the observed SCD. Furthermore, the hERG *in vitro* experiments were conducted per best practices (ICH S7B Q&A 2.1) and therefore support an integrated risk

assessment (ICH S7B Q&A 1.1 and 1.2) together with the clinical data to exclude a small mean increase in the QTc interval for the therapeutic dose.

2 Internal Comments for the Division

Not applicable.

3 BACKGROUND

The sponsor provided raw data from cardiac ion channel studies (TT209425FIN and TT204803FIN). Results from our independent analysis of the submitted electrophysiology data are consistent with the sponsor's results, with no significant changes in IC_{50}s. In addition, we consider the results at 1 Hz more representative of the effects on the hERG channel because there were limitations in the hERG experiment at 0.033 Hz (section 4.1.2.1.1).

Thus, safety margins of vericiguat and M1 metabolites against major cardiac ion channels are expected to be larger than 554x and 227x, respectively (see Appendix 4.1). These findings support that vericiguat and its major metabolite do not directly interact with the cardiac ion channels including hERG, Nav1.5 and IKs at the therapeutic exposure. In our previous review of the clinical data (DARRTS 08/25/2020) we concluded that the clinical data only supported excluding large mean increases in the QTc interval due to limitations of the study design and limited nonclinical data that could not support an integrated risk assessment. The results of the hERG evaluation reviewed in the current submission address the limitations of the prior hERG assay and provide a sufficient safety margin for both vericiguat and the M1 metabolite.

In conclusion, the totality of nonclinical and clinical evidence supports excluding a small increase in the QTcF interval and we therefore propose new labeling language for section 12.2:

Cardiac Electrophysiology

(b) (4) integrated risk assessment of nonclinical and clinical data supports that administration of verciguat 10 mg is not associated with clinically meaningful QTc prolongation.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

4 Appendices

4.1 APPENDIX I: REVIEW OF SUPPORTING NONCLINICAL DATA

The sponsor evaluated the effects of vericiguat (BAY1021189) and its M1 metabolite (BAY1222707) on hERG and Nav1.5 currents using manual whole cell patch clamp methods and on KvLQT1/minK currents (IKs) using automated patch clamp methods in HEK293 cells. We previously reviewed the sponsor's ion channel study protocols (see our prior review, link) and provided recommendations for hERG, Nav1.5 and KvLQT1/minK experiments, including changes to ensure that the Nav1.5 experiments reflect "worst case scenario", i.e., depolarized holding potential (at -70 mV) at fast pacing rate (3 Hz) to mimic depolarized myocyte membrane potential and elevated heart rate in patients with heart failure (link).The sponsor implemented the suggested changes in the final protocol. Furthermore, the hERG assay at 1 Hz follows the recommended best practice for in vitro experiments described in ICH S7B Q&A (section 2.1).

4.1.1 Sponsor's submission

4.1.1.1 hERG assay

The ion channel report (Study ID: TT209425FIN, link) describes the potential effects of vericiguat and its M1 metabolite on the hERG current in HEK293 cells. The hERG current was assessed at physiological temperature (37 ± 1 ºC), using a voltage protocol that is recommended by the FDA (link). The effects of vericiguat and M1 metabolite on hERG current amplitude were examined at pacing rates of 0.033 Hz (every 30 seconds) and 1 Hz (every 1 second) to characterize the rate dependence of current inhibition. For current measurements, 3 traces were averaged before (control) and after a steady-state had been reached. At pacing rate of 1 Hz, the positive control drug (dofetilide) inhibited hERG currents by 11%, 35% and 99% at 0.1, 1 and 10 nM, respectively. At pacing rate of 0.033 Hz, dofetilide inhibited the hERG currents by 4%, 10% and 99% at 0.1 nM, 1 and 10 nM, respectively. Samples of the test article formulation solutions collected from the cell chamber in a satellite experiment were analyzed for concentration verification. The results from the sample analysis indicated that the measured concentrations of vericiguat at all test concentrations were within ± 15.0% of nominal concentrations, thereby meeting the acceptance criteria and nominal concentrations were used to describe drug effects. Measured concentrations of the M1 metabolite tended to be higher (from 115% to 144%) than the nominal concentrations. Nominal concentrations were used describe drug effect for the M1 metabolite. Drug concentration was not verified for dofetilide. Series resistance compensation and rundown correction were not mentioned in the study report. The study results from the sponsor's report are summarized in Table 1.

Reviewer's comment: *Review of the data shows that steady-state was only reached for the 1 Hz experiments, see section 4.1.2.1 for details.*

Table 1. Summary of IC_{50}s of vericiguat and M1 metabolite on hERG current (Table 1 to Table 4 in study TT209425FIN)

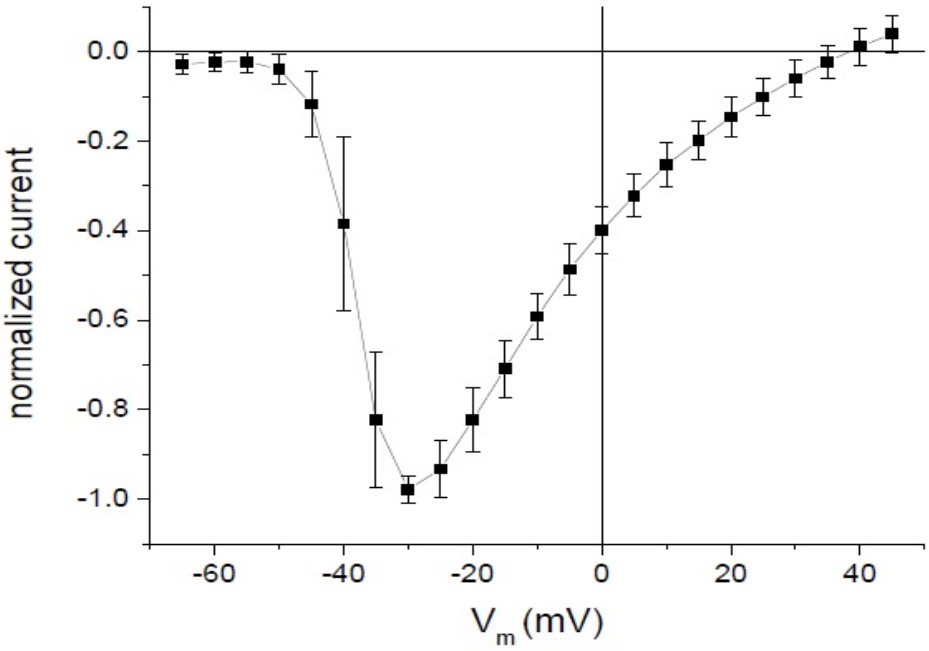
	Vericiguat IC_{50} (µM)	M1 metabolite IC_{50} (µM)
1 Hz	>10 (~20% block)	>10 (~6% block)

0.033 Hz	2.9	>10 (~3% block)

4.1.1.2 Nav1.5 assay

In the study TT209425FIN (link), the sponsor also evaluated the effects of vericiguat and its M1 metabolite on peak Nav1.5 current at a depolarized holding potential (-80 mV), at a fast pacing rate (3 Hz). In a pilot set of experiments, a holding potential of -70 mV was tried. The current amplitude was either very small or the current was dramatically reduced upon rapid pacing in the absence of test compound. The experiments were conducted at 37 ± 1 °C, using a protocol with a depolarizing step to -15 mV (20 ms) from a holding potential of -80 mV, repeated at 0.33 s intervals. Before running this pharmacology experiment, a separate file characterizing IV relationship (from -65 mV to 45 mV in 5 mV increment) was obtained to illustrate adequate voltage control at 37°C (Figure 1). This IV relationship indicates adequate voltage control have been achieved under the experimental conditions. For current measurements, 3 traces were averaged before (control) and after a steady-state had been reached. The positive control drug (flecainide) inhibited hERG currents by 30%, 72% and 96% at 1, 3 and 10 µM, respectively. The results confirm the sensitivity of the test system to Nav1.5 inhibition. The study results are summarized in Table 2.

Figure 1. Current-voltage relationship under physiological temperature (Appendix 3, in study report TT209425FIN)



Reviewer's comment: *Nav1.5 assay was assessed at the holding potential of -80 mV rather than at the recommended -70 mV since significant current reduction was observed at -70 mV in a pilot experiment. The large error bars between -45 mV to -35 mV in the I-V curve may indicate inadequate voltage control under experiment conditions. However, review of the data shows adequate voltage control has been reached. The difference between our analysis and sponsor's*

may result from the uses of different peak Nav1.5 current measurement methods. See section 4.1.2.2 for details.

Table 2. Summary of IC_{50}s of vericiguat and M1 metabolite on Nav1.5 current (Table 7 and Table 8 in study report TT209425FIN)

	Vericiguat IC_{50} (μM)	M1 metabolite IC_{50} (μM)
3 Hz	>10 (~3% block)	> 10 (~2% block)

4.1.1.3 KvLQT1/minK assays

A characterization of the effects of vericiguat and M1 metabolite on KvLQT1/minK (IKs) was attempted using manual patch clamp technique as part of the study's design. However, excessive run down at 37° C made it impossible to test the effects of vericiguat and M1 on IKs using manual patch clamp technique. In an effort to generate data with vericiguat and M1 metabolite, experiments were performed at room temperature using the Qpatch automated patch clamp system.

The study report TT204803FIN (link) describes the potential effects of vericiguat and its M1 metabolite on the IKs using an automated Qpatch system in HEK293 cells. On each plate, 18 wells were assigned to the test article, 18 wells to vehicle controls, and 12 wells to the positive control bepridil (10 μM). All articles were tested at 10 μM added with three repeat additions to insure complete solution exchange. IKs was assessed at room temperature, using a voltage protocol consisting of a hyperpolarizing step from -50 mV to +50 mV (3 s), followed by a repolarizing step to -50 mV (3 s). The voltage waveform was repeated every 10 seconds (0.1 Hz) or every 30 seconds (0.033 Hz). For peak tail current measurements, the current amplitudes from the last 3 pulses were averaged at the end of each treatment period: vehicle baseline (5 min), drug wash on (7.5 min). The positive control drug (10 μM bepridil) inhibited IKs by 58% and 61%, at pacing rate of 0.1 Hz and 0.033 Hz, respectively. Samples of the test article formulation solutions collected from the compound plate (before the perfusion chamber) were analyzed for concentration verification. The results from the sample analysis indicated that the measured concentrations of vericiguat at all test concentrations were within ± 15.0% of nominal concentrations, thereby meeting the acceptance criteria and nominal concentrations were used to describe drug effects. Study results are summarized in Table 3.

Table 3. Summary of IC_{50}s of vericiguat and M1 metabolite on IKs current (Table 1 in study report TT204803FIN)

	Vericiguat IC_{50} (μM)	M1 metabolite IC_{50} (μM)
0.1 Hz	>10 (-2.9% block)	>10 (-0.1% block)
0.033 Hz	>10 (-1.3% block)	>10 (2.7% block)

4.1.2 Reviewer's assessment and data re-analysis

Original electrophysiology records for ion channel studies were provided by the sponsor. We reanalyzed raw data of hERG, Nav1.5 and IKs assays in study report TT209425FIN to assess

data quality and verify study report conclusions. For data quality assessment, holding current from all traces were examined to verify stability, and time course plots were constructed to verify that current amplitude in control solution were stable prior to drug application, and that drug effects reached steady state.

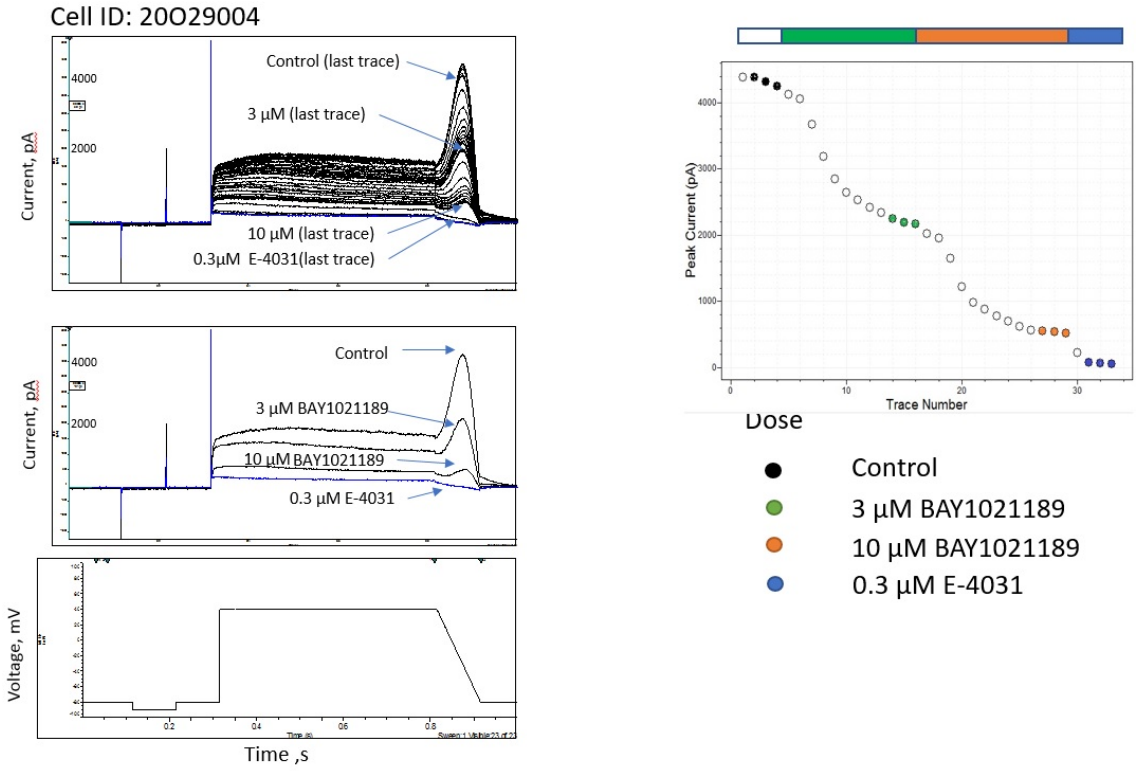
4.1.2.1 The hERG assays

The sponsor provided raw data for the hERG assay at 1.0 Hz and 0.033 Hz. The sponsor used the voltage protocol that is recommended by the FDA (link). The hERG current was assessed at physiological temperature (37 °C).

4.1.2.1.1 Assays at 0.033 Hz

Representative analysis of vericiguat on hERG current at 0.033 Hz from one cell (Cell ID: 20O29004) is shown in Figure 2. The top left panel shows all recorded traces from this cell; the middle left panel shows the last trace of each application; the bottom left panel, voltage waveform used to evoke hERG current. Time course plot of hERG current is shown on the right panel. Traces recorded in control solution are shown in white bar, following 3 µM vericiguat application in green and 10 µM vericiguat application in orange; and following application of E-4031, a selective hERG blocker, in blue.

Figure 2. Representative hERG experiment at 0.033 Hz from cell 20O29004



HERG current amplitudes from the last 3 traces acquired in control (black solid circles) and in drug solutions (green and orange solid circles) were then averaged to calculate % inhibition by that concentration. E-4031 (0.3 µM) was added at the end of the experiment to show the residual current in a few cells. In the cells where E-4031 was added, the residual (non-hERG) current was small compared to control. Therefore, non-hERG current subtraction was not performed since

remaining residual current after E-4031 addition (blue solid circles) was negligible relative to peak hERG current in control (Figure 2). Nominal concentration-inhibition plots were generated, and the individual datapoints fit with the Hill equation to calculate IC_{50} and Hill coefficient using the following equation:

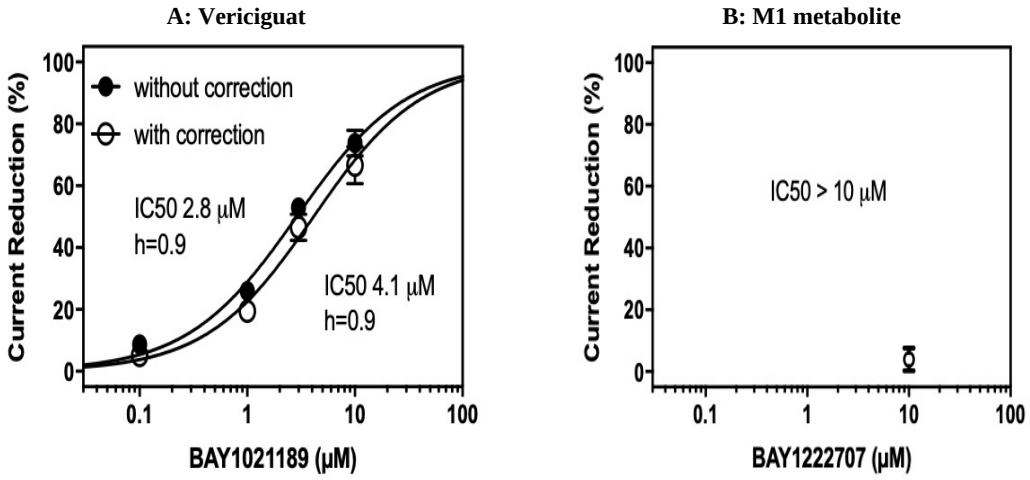
$$\%\ block\ =\ 100 \times (1 - \frac{1}{1 + (\frac{c}{IC50})^{nH}})$$

where *C* is the drug concentration, *IC_{50}* is the concentration that causes 50% reduction of the current, and n_H is the hill coefficient. The minimal and maximal % inhibitions were constrained at 0 and 100%.

The sponsor only recorded less than 5 traces in control in 13 out of 22 cells. The current stability (steady state) cannot be determined in those cells. In addition, there are visible current rundown in 9 out of 15 some cells in vericiguat group. Therefore, rundown correction by a linear fit was performed in the cells with rundown .

The calculated IC_{50} values of vericiguat were 4.1 µM and 2.8 µM, with and without rundown correction, respectively (Figure 3A). The metabolite M1 metabolite inhibited the hERG current by 3.9% at 10 µM (Figure 3B). Our results are similar to those in the study reports (Table 1). The positive control dofetilide at 0.1, 1 and 10 nM inhibited the hERG current by 4.8%, 9% and 96%, at 0.033 Hz, respectively. The calculated IC_{50} value for dofetilide on hERG current at 0.033 Hz was 2.6 nM.

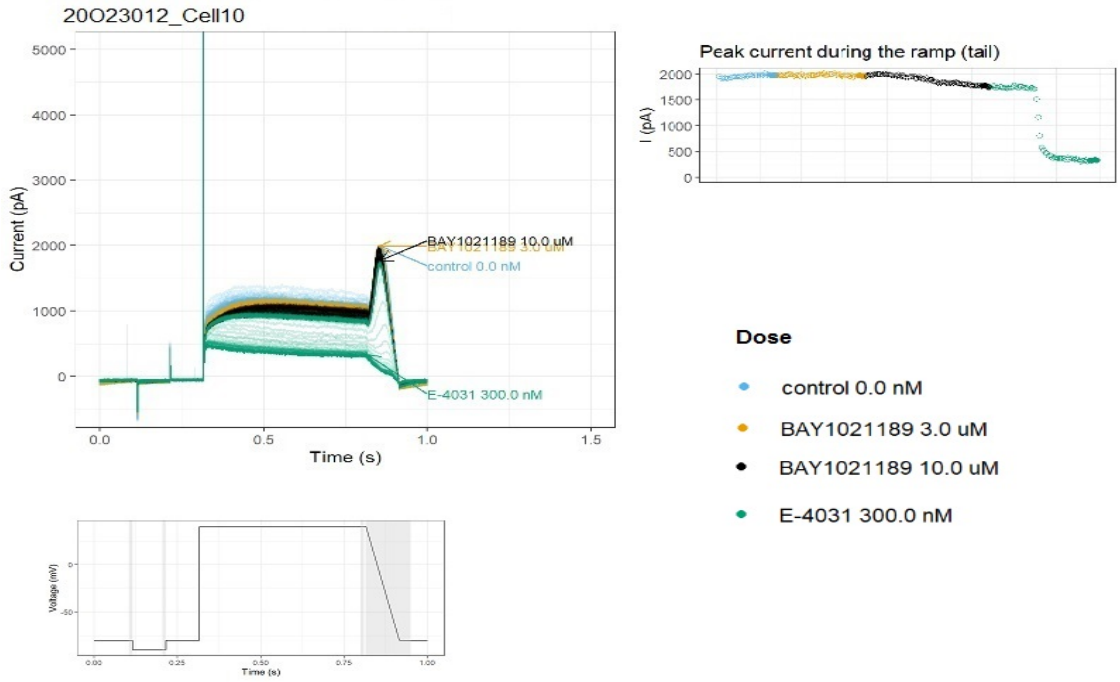
Figure 3. Concentration-response curve of vericiguat and M1 metabolite on hERG current



4.1.2.1.2 Assays at 1.0 Hz

Representative analysis of vericiguat on hERG current at 1 Hz from one cell (Cell ID: 20O23012-Cell10) is shown in Figure 4. The top left panel shows all recorded traces from this cell; the bottom left panel is the voltage waveform used to evoke hERG current (shaded gray region highlights where peak hERG tail current was measured). Traces recorded in control solution are shown in blue, following 3 µM vericiguat application in orange and 10 µM vericiguat application in black; and following application of E-4031, a selective hERG blocker, in green. Time course plot of hERG current is shown on the right panel.

Figure 4. Representative hERG experiment at 1 Hz from cell 20O23012_Cell10 for vericiguat (BAY1021189)



HERG current amplitudes from the last 5 traces acquired in control (blue solid circles) and in drug solutions were then averaged to calculate % inhibition by that concentration. Data with or without E-4031 subtraction were calculated to compare the drug's effect. Results showed that vericiguat had similar values of % inhibition with or without residual current subtraction. For consistency with the data analysis at 0.033 Hz, data without E-4031 subtraction at 1.0 Hz are shown in this appendix. On average, vericiguat inhibited hERG current by 1.9% at 3 µM, and 18.9% at 10 µM. The estimated IC_{50} value for vericiguat on hERG is 28.3 µM. The M1 metabolite inhibited hERG current by 6% at 10 µM (Table 4). The positive control dofetilide at 0.1, 1 and 10 nM inhibited the hERG current by 11.3%, 34% and 90%, at 1.0 Hz, respectively. The calculated IC_{50} value for dofetilide on hERG current at 1.0 Hz was 1.6 nM.

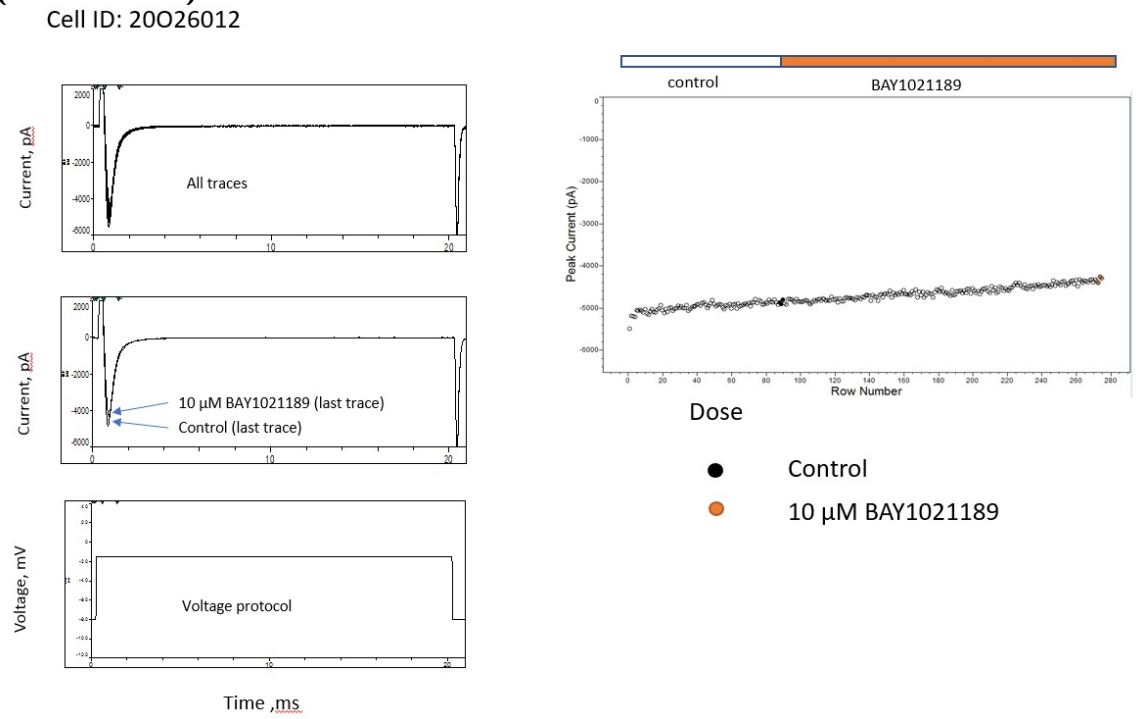
Table 4. Inhibition (%) of tested articles on hERG current at 1.0 Hz.

Substance	N	Mean (%)	SD (%)	SEM (%)
Vericiguat 3.0 uM	4	-1.9	1.7	0.9
Vericiguat 10.0 uM	5	-18.9	8.0	3.6
Vericiguat 10.0 uM	4	-6.0	3.6	1.8
Dofetilide 0.1 nM	3	-11.3	6.8	3.9
Dofetilide 1.0 nM	3	-33.7	6.0	3.5
Dofetilide 10.0 nM	3	-90.2	4.3	2.5
E-4031 300.0 nM	10	-86.4	6.3	2.0

4.1.2.2 Nav1.5 assays

Data analysis for this current is similar to that for hERG current. Representative analysis of vericiguat on Nav1.5 peak current at 3 Hz from one cell (Cell ID: 20O26012) is shown in Figure 5. The top left panel shows all recorded traces from this cell; the middle left panel shows the last trace of each application; the bottom left panel, voltage waveform used to evoke hERG current. Time course plot of Nav 1.5 current is shown on the right panel. Traces recorded in control solution are shown in white bar, following 10 µM vericiguat application in orange. No selective Nav1.5 inhibitor was used in the end of the experiment.

Figure 5. Representative Nav1.5 experiment at 3 Hz from cell 20O26012 for vericiguat (BAY1021189)



Before running this pharmacology experiment, a separate file characterizing the current-voltage relationship (from -65 mV to 45 mV in 5 mV increment) was obtained to demonstrate voltage control at 37ºC (Figure 6). The results show that adequate voltage controls had been achieved under the experimental conditions (37ºC). We noticed that our I-V result is different from what the sponsor reported (Figure 1). The difference between our results and the sponsor's may result from the uses of different methods in measuring the peak Nav1.5 current at each voltage. As seen in Figure 7, the result of I-V curves are different between one cursor measurement (measure the Nav1.5 current amplitude at the cursor) and two cursor measurement (measure the peak Nav1.5 current between two cursors) in the same recording. Two cursor measurement was used in our analysis. Since the shape of I-V curve of sponsor's is similar to the shape of I-V curve with one cursor measurement (Figure 7C). The sponsor might have used the one cursor measurement in the analysis. We suspect this is the origin of the difference between our results and the sponsor's.

Figure 6. I-V curve of Nav1.5 current at physiological temperature

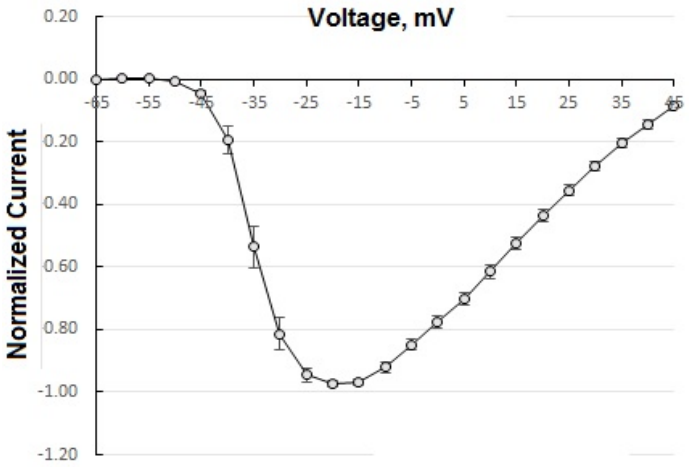
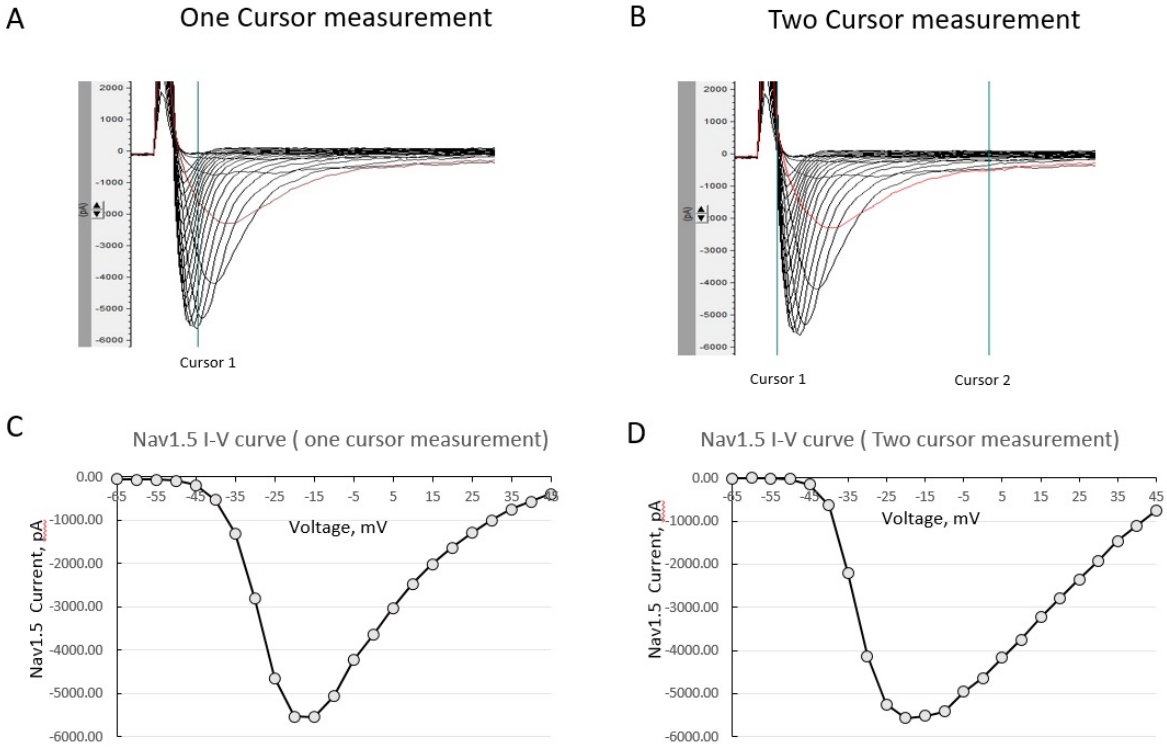


Figure 7. I-V curve with two different Nav1.5 current measurements in the same recording (Cell ID: 20O26011).



Vericiguat inhibited Nav1.5 current by 3.8% at 10 µM. The M1 metabolite inhibited hERG current by 0.7% at 10 µM. The results are similar to the study report (Table 2). The positive control flecainide at 1,3 and 10 µM inhibited the Nav1.5 current by 32%, 74% and 97%, at 3 Hz, respectively. The calculated IC_{50} for flecainide on Nav1.5 current was 2.4 µM.

4.1.2.3 KvLQT1/minK assays

The sponsor provided raw data for the IKs assay. Experiments were assessed at room temperature since stable recordings could not be obtained with KvLQT1/minK channels at 37 °C due to excessive rundown in current. The experiments were performed in an automated patch clamp platform (Qpatch system) using a voltage protocol consisting of a hyperpolarizing step from -50 mV to +50 mV (3 s), followed by a repolarizing step to -50 mV (3 s). The voltage waveform was repeated every 10 seconds (0.1 Hz) and every 30 seconds (0.033 Hz).

Representative analysis of vericiguat on IKs at 0.1 Hz and 0.033 Hz are shown in Figure 8 and Figure 9, respectively. The top left panel of Figure 8 or Figure 9 shows the last trace in the absence (control) and in the presence of 10 µM of vericiguat; the bottom left panel is the voltage waveform used to evoke IKs, with the shaded gray area highlighting where the IKs tail current is measured. Time course plot of IKs is shown on the right panel. Traces recorded in control solution are shown in white bar, following 10 µM vericiguat application in orange; and following application of control solution (washout) again in the end of the experiment.

Figure 8. Representative IKs experiment at 0.1 Hz from cell 739.1.1 for vericiguat (BAY1021189)

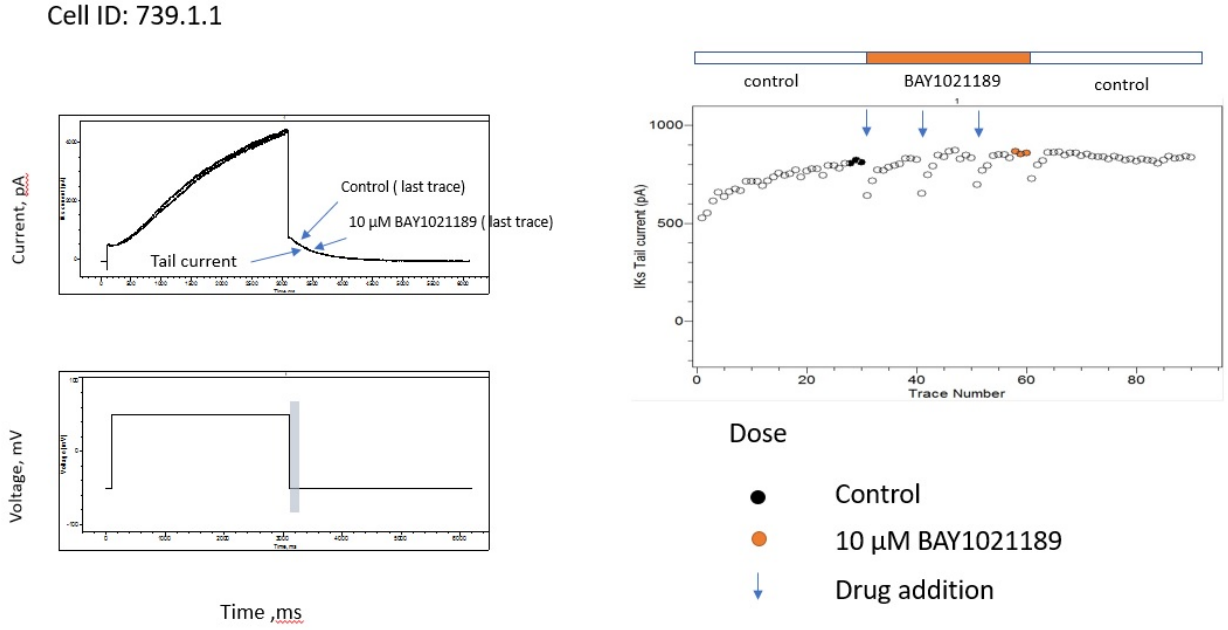
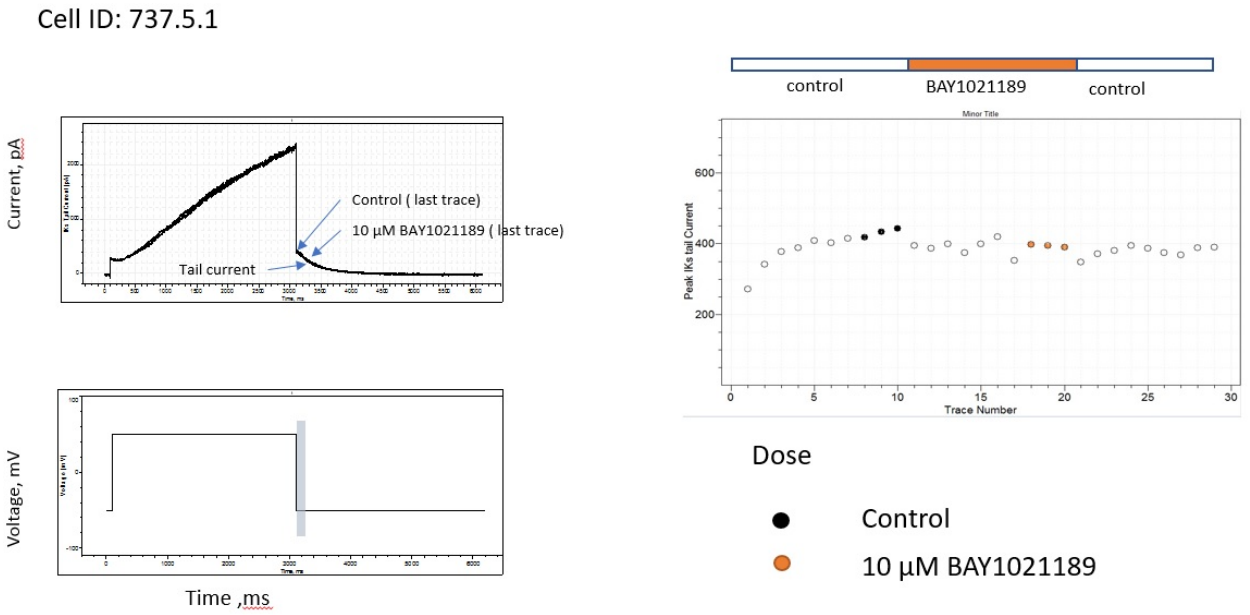


Figure 9. Representative IKs experiment at 0.033 Hz from cell 737.5.1 for vericiguat (BAY1021189)



IKs amplitudes from the last 3 traces acquired in control (black solid circles) and in drug solution (orange solid circles) were then averaged to calculate % inhibition by that concentration. On average, vericiguat at 10 µM inhibited IKs by -3.8% and -0.2%, at 0.1 Hz and 0.033 Hz, respectively. The M1 metabolite at 10 µM inhibited IKs by 0.3% and 4.4% , at 0.1 Hz and 0.033 Hz, respectively. The positive control bepridil at 10 µM inhibited the IKs by 57.9% and 64.9% at 0.1 Hz and 0.033 Hz, respectively.

4.1.3 Summary

The effects of vericiguat and M1 metabolite on hERG, Nav1.5 and IKs are compared below (Table 5).

Table 5. Summary of vericiguat and M1 metabolite on hERG and Nav1.5 currents (IC_{50} values per FDA analysis)

	hERG IC_{50}		Nav1.5 IC_{50}	IKs IC_{50}	
	1.0 Hz	0.033 Hz	3 Hz	0.1 Hz	0.033 Hz
Vericiguat (µM)	28.3	2.8, 4.1[1]	> 10 (3.8%)	>10 (-3.8%)	>10 (-0.2%)
M1 metabolite (µM)	>10 (6.0%)	> 10 (3.9%)	> 10 (0.7%)	> 10 (0.3%)	> 10 (4.4%)
Dofetilide (nM)	1.6	2.6	N/A	N/A	N/A
Flecainide (µM)	N/A	N/A	2.4	N/A	N/A
Bepridil (µM)	N/A	N/A	N/A	57.9% (at 10 µM)	64.9% (at 10 µM)

[1] IC_{50} value was corrected for current rundown

While there are numerical differences in the results from our independent analysis compared to the sponsor's, the information from our analysis is consistent with the sponsor's conclusions and

we have not observed significant changes in IC_{50}s. However, we disagree with the reverse use dependence conclusion (e.g. vericiguat blocked hERG current more potent at 0.033 Hz than at 1 Hz) by the sponsor since there were limitations in the hERG experiment at 0.033 Hz. For example, data at 0.033 Hz had a tendency to overestimate the IC_{50} value due to significant current rundown. In addition, recording quality cannot be assessed as current recordings from raw data showed that there were less than 5 traces in most of cells in control at 0.033 Hz. Therefore, we consider the results at 1 Hz more representative of the effects on the hERG channel.

The safety margins of vericiguat and metabolite on hERG, Nav1.5 and IKs are summarized in the Table 6.

Table 6. Summary of safety margins of vericiguat and M1 metabolite on cardiac ion channels

	Safety Margin		
	hERG	Nav1.5	KvLQT1/minK
Vericiguat	1572x	>554x (3.8% at 10 µM)	>554x (-3.8% at 10 µM)
M1 metabolite	>227x (6.0% at 10 µM)	>227x (0.7% at 10 µM)	>227x (0.3% at 10 µM)

Vericiguat: Cmax was 350 ng/mL, PPB was 97.8%. Free Cmax was 7.7 ng/mL (18 nM)
M1 metabolite: Free Cmax was 26.5 ng/mL (44 nM).
hERG, Nav1.5 and IKs safety margins were assessed at 1 Hz, 3 Hz and 0.1 Hz, respectively.

In conclusion, vericiguat and its major metabolite do not directly interact with the cardiac ion channels including hERG, Nav1.5 and IKs at the therapeutic exposure.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LARS JOHANNESEN
01/07/2021 11:00:59 AM
Primary nonclinical review by Dr. Donglin Guo

JOSE VICENTE RUIZ
01/07/2021 11:27:29 AM

DONGLIN GUO
01/07/2021 11:33:20 AM

CHRISTINE E GARNETT
01/07/2021 12:52:30 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 23, 2020

To: Alexis Childers, Senior Regulatory Health Project Manager
Cardiology and Nephrology / Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, & Nephrology

Michael Monteleone, Associate Director for Labeling
Division of Cardiology and Nephrology (DCN)

From: Zarna Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for VERQUVO™ (vericiguat) tablets, for oral use

NDA/BLA: 214377

In response to DCN consult request dated June 19, 2020, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and the carton and container labeling for VERQUVO™ (vericiguat) tablets, for oral use.

Labeling: OPDP received the initial draft labeling for review by electronic mail from DCN (Alexis Childers) on December 15, 2020. OPDP's comments on the proposed labeling are based on the attached updated draft labeling available on DCN's SharePoint on December 23, 2020 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on December 23, 2020.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on December 7, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Zarna Patel at (301) 796-3822 or zarna.patel@fda.hhs.gov.

24 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ZARNA PATEL
12/23/2020 04:44:08 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 23, 2020
To:	Alexis T. Childers, RAC, CQIA Senior Regulatory Project Manager **Division of Cardiology and Nephrology (DCN)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Zarna Patel, Pharm D Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	VERQUVO (vericiguat)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 214377
Applicant:	Merck Sharp & Dohme Corp.

1 INTRODUCTION

On May 20, 2020, Merck Sharp & Dohme Corp. submitted for the Agency's review an original New Drug Application (NDA) 214377 for VERQUVO (vericiguat) tablets. The proposed indication for VERQUVO (vericiguat) tablets is to reduce the risk of cardiovascular death and 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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiology and Nephrology (DCN) on June 18, 2020 and June 19, 2020, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for VERQUVO (vericiguat) tablets. The Applicant originally proposed a Patient Package Insert (PPI) with their application. On December 2, 2020, the DCN requested by email that the Applicant convert their proposed PPI to a Medication Guide (MG) and submit it for review and approval as part of the labeling for VERQUVO (vericiguat) tablets.

2 MATERIAL REVIEWED

- Draft VERQUVO (vericiguat) tablets MG received on December 7, 2020, and received by DMPP on December 15, 2020.
- Draft VERQUVO (vericiguat) tablets Prescribing Information (PI) received on May 20, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on December 15, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHARON R MILLS
12/23/2020 03:16:27 PM

ZARNA PATEL
12/23/2020 03:19:23 PM

BARBARA A FULLER
12/23/2020 04:30:19 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 15, 2020
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214377
Product Name and Strength:	Verquvo (vericiguat) tablets, 2.5 mg, 5 mg and 10 mg
Applicant/Sponsor Name:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
OSE RCM #:	2020-1052-2
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on December 7, 2020 for Verquvo. We reviewed the revised container labels for Verquvo (Appendix A) to determine if it is acceptable from a medication error perspective. It was determined by the review team to convert the Patient Information (PPI) to a Medication Guide (MG). In response, the Applicant revised the container labels to include the Medication Guide statement on the principal display panel.

2 CONCLUSION

We find the proposed container labels acceptable from a medication error perspective and we have no additional recommendations at this time.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MAXIMILIAN STRAKA
12/15/2020 12:53:35 PM

HINA S MEHTA
12/16/2020 02:55:02 PM

Clinical Inspection Summary

Date	November 17, 2020
From	Tina Chang, M.D., Reviewer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Tzu-Yun McDowell, M.D., Clinical Reviewer Preston Dunnmon, M.D., M.B.A, Clinical Team Leader Norman Stockbridge, M.D., Ph.D., Director Alexis Childers, RAC, CQIA, Sr. Regulatory Project Manager Division of Cardiology and Nephrology (DCN)
NDA #	214377
Applicant	Merck Sharp and Dohme Corp.
Drug	Verquvo (vericiguat)
NME	Yes
Therapeutic Classification	Soluble guanylate cyclase (sGC) stimulator
Proposed Indication	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 therapies
Consultation Request Date	June 18, 2020
Summary Goal Date	December 20, 2020
Action Goal Date	January 20, 2021
PDUFA Date	January 20, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from a single study (Protocol P001MK1242) was submitted to the Agency in support of a New Drug Application (NDA 214377) for Verquvo (vericiguat) 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 therapies. 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 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.

II. BACKGROUND

Vericiguat is an oral soluble guanylate cyclase (sGC) stimulator in development for treatment of chronic heart failure (HF) with reduced ejection fraction. In patients with HF, endothelial dysfunction and oxidative stress may reduce nitric oxide (NO) bioavailability, resulting in insufficient sGC stimulation and reduced sGC -derived cyclic guanosine monophosphate (cGMP) synthesis.

The applicant, Merck Sharp and Dohme Corp., submitted the data from a randomized, double-blind, placebo-controlled trial (Protocol P001MK1242), to compare the efficacy and safety of the addition of vericiguat to placebo on a background of HF standard of care in the time to first occurrence of the composite of cardiovascular (CV) death or HF hospitalization in male and female subjects aged 18 years or older with chronic HF with reduced ejection fraction (<45%). The following describes briefly the Protocol P001MK1242.

Protocol P001MK1242

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

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

The primary efficacy endpoint was the time to first occurrence of the composite of cardiovascular death or HF hospitalization.

The study randomized 5050 subjects from 694 sites in 42 countries. The first subject was randomized on 25 September 2016 and the last patient completed the study on 2 September 2019.

Rationale for Site Selection

The clinical investigators (Dr. Hans Prozesky, Site 1912 and Dr. Clara Saldarriaga, Site 0501) were selected using risk-based approach that also considers numbers of enrolled subjects and treatment effect.

III. RESULTS:

1. **Hans Prozesky, M.D.**
   TREAD Research
   Francie van Zijl Drive, Room 41, 8th Floor
   Tygerberg Hospital
   Parow, Cape Town, Western Cape 7500
   South Africa
   Remote regulatory assessment dates: 20 August – 9 September 2020

   Dr. Hans Prozesky has no previous inspection history with the FDA. This was his first FDA GCP compliance assessment.

   A remote regulatory assessment (in lieu of a full CI GCP site inspection) was conducted for this site in South Africa due to travel restrictions during the COVID-19 pandemic. Video conferencing via Webex and document sharing via an online platform (box.com) were utilized to exchange information in support of regulatory compliance review.
   For Protocol P001MK1242, 135 subjects were screened and 110 subjects were enrolled at this site. Among the 135 enrolled subjects, 32 subjects were withdrawn due to death and 78 subjects completed the study.

   Due to staff limitations with scanning records at the site, remote assessment reviewed 4 subject's source records comprehensively, and 30 subject's source records (15 subjects each in the vericiguat and placebo groups) for the primary efficacy endpoint and adverse events.

   The remote regulatory assessment evaluated the following documents: the protocol and protocol amendments, sponsor and clinical investigator agreements, financial disclosures, subject medical histories, concomitant medications, inclusion/exclusion criteria, central and local laboratory results, echocardiogram results, ECGs, physical examinations and blood pressure/pulse rates utilized for dose titration, dose interruptions and resumptions, AEs/SAEs and subject follow-up, and related documentation submitted to and from the adjudication committee.

   The primary efficacy endpoint data in the subjects' source documents (raw data) were verified against the data line listings provided by the sponsor, and no discrepancies were noted. There was no evidence of underreporting of adverse events.

2. Clara Saldarriaga, M.D.
Centro Cardiovascular
Colombiano Clinical Santa Maria
Calle 78 B # 75-21, Piso 4
Medellin, Antioquia 50034
Colombia
Remote regulatory assessment dates: July 22-August 5, 2020

Dr. Clara Saldarriaga has no previous inspection history with the FDA; this was her first FDA GCP compliance assessment.

A remote regulatory assessment (in lieu of a full CI GCP site inspection) was conducted for this site due to travel restrictions during the COVID-19 pandemic. The entire investigation was conducted remotely through WebEx meetings at mutually agreed upon times. Original records were primarily in Spanish, both in hardcopy paper form (i.e. CRFs, ICFs, ECGs, Laboratory Records) and electronic Hospital Medical Record forms (Subject Medical Histories and other Hospital records) accessible by the firm and uploaded to the Box.com account licensed to the FDA.

For Protocol P001MK1242, 50 subjects were screened and 42 subjects were enrolled at this site. An additional 17 subjects transferred to Dr. Saldarriaga's Site #0501 from Sites #0508 and #0515 in Medellin that closed. Among the 59 total subjects, 12 subjects died, and 47 subjects completed the study.

Due to staff limitations with scanning records at the site, remote assessment reviewed 3 subject's source records comprehensively, and 15 subject's source records (8 subjects in the vericiguat group and 7 subjects in the placebo group) for the primary efficacy endpoint and adverse events.

The remote regulatory assessment evaluated the following documents: the protocol, protocol amendments, informed consent forms, Sponsor/Monitor/EC communications, pertinent notes to file, delegation of duties, screening and enrollment log, Inclusion/Exclusion criteria, central and local laboratory results, echocardiogram results, physical examinations and blood pressure/pulse rates utilized for dose titration, medical histories for screening, dose interruptions and resumptions, AEs/SAEs, and monitor reports

The primary efficacy endpoint data in the subjects' source documents (raw data) were verified against the data line listings provided by the sponsor, and no discrepancies were noted. There was no evidence of underreporting of adverse events.

{See appended electronic signature page}

Suyoung Tina Chang, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm.
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
OSI/DCCE/GCP Reviewer/
OSI/ GCP Program Analysts/
OSI/Database PM/Dana Walters

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUYOUNG T CHANG
12/10/2020 03:56:30 PM

MIN LU
12/10/2020 06:00:20 PM

KASSA AYALEW
12/11/2020 02:19:26 PM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates

Date:	10/29/2020
Reviewer:	Yan Li, PhD, B.Pharm Division of Epidemiology II
Team Leader (Acting):	Marie Bradley, PhD, MPharm, MSc.PH Division of Epidemiology II
Deputy Director (Acting):	Efe Eworuke, PhD, MSc., B.Pharm Division of Epidemiology II
Deputy Director:	Michael Nguyen, MD Sentinel Program
Deputy Director:	Robert Ball, MD, MPH Office of Surveillance and Epidemiology
Subject:	ARIA Sufficiency Memo
Drug Name:	Vericiguat (Verquvo)
Application Type/Number:	NDA 214377
Applicant/sponsor:	Merck

1. BACKGROUND INFORMATION

1.1. Medical Product

NDA 214377 is being reviewed for vericiguat (Verquvo), a soluble guanylate cyclase (sGC) stimulator, for the proposed indication of reducing 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%. sGC catalyzes the synthesis of intracellular cyclic guanosine monophosphate (cGMP). Deficiencies in sGC-derived cGMP contribute to myocardial and vascular dysfunction. Vericiguat can restore this deficiency by directly stimulating sGC, interpedently of and synergistically with nitric oxide, to augment the levels of intracellular cGMP which may improve both myocardial and vascular function.

1.2. Describe the Safety Concern

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. 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.

There are no available data with vericiguat use in pregnant or lactating women. Subjects were excluded from phase 2b and phase 3 clinical trials if they were pregnant or breastfeeding, or planning to become pregnant or breastfeeding. During these trials, no pregnancies were reported among exposed female subjects or female partners of exposed subjects.

Riociguat (Adempas), another agent within the sGC stimulator drug class, was approved in 2013 for the treatment of persistent/recurrent chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension. Preclinical data showed that riociguat is a potential teratogen as it is associated with ventricular septal defects and bone malformations in rat studies. As a result, it is approved with a Risk Evaluation and Mitigation Strategy (REMS) to ensure its benefit outweigh the risk of embryo-fetal toxicity in females of reproductive potential. As of September 19, 2019, the sponsor reported a total of 30 riociguat exposed pregnancies worldwide, including nine in the United States. Among these cases, nine resulted in pregnancy termination and six resulted in spontaneous abortion. No fetal abnormalities were reported in any of these 15 cases. One case of ectopic pregnancy was reported which ended up with salpingectomy. Furthermore, there was one case of patent foramen ovale in a premature infant (which may close in the future and then would not be considered a heart defect), and one healthy baby. Pregnancy outcomes for the remaining 12 cases were unknown.[1]

[1]Periodic safety update report. ADEMPAS® BAY 63-2521 (Riociguat). No. 9.0. \\CDSESUB1\evsprod\nda204819\0167\m5\53-clin-stud-rep\536-postmark-exp\pbrer-20sep2018-to-19sep2019.pdf

Although embryo-fetal toxicity seems to be a class effect of sGC stimulators, the REMS oversight committee determined that the labelling can adequately mitigate this risk for vericiguat and a REMS is not warranted. There are two main reasons for this decision. First, the majority of intended population for vericiguat are older females with no reproductive potential. Requiring a REMS can create potential burden of access to these patients. Second, other products (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, angiotensin receptor neprilysin inhibitor, ivabradine) used as the standard of care for heart failure with reduced ejection fraction (HFrEF) include embryo-fetal toxicity risks in labeling, and do not have a REMS.

To further support the decision of not issuing a REMS, we conducted an analysis in the Sentinel system to estimate the prevalence of HF in women of child-bearing age and the number of pregnancies among these patients. Using data from six large data partners in the Sentinel system from January 2010 to February 2020, we identified a total of 144,162 HF patients among 29.6 million women of child-bearing age (prevalence, 0.5%). Within this HF cohort, there were 813 women with 822 pregnancies ending in live birth deliveries (5.7 live birth deliveries per 1,000 women with HF). Using a more specific algorithm targeted at identifying HFrEF patients, we identified 39,844 women with HFrEF (prevalence, 0.1%) including 221 women with 223 pregnancies ending in live birth deliveries (5.5 live birth deliveries per 1,000 women with HFrEF). Across different calendar years, the rate of deliveries ranged from 2.6 to 3.6 live birth deliveries per 1,000 women with HF and from 1.8 to 3.5 live birth deliveries per 1,000 women with HFrEF. Including stillbirth deliveries barely changed our estimates.

Applying the prevalence of HF and HFrEF to the 2019 Census estimates, we projected there were 310,613 women with HF and 85,254 women with HFrEF in the United States in 2019. Among these women, projected numbers of pregnancies ending in live birth deliveries were 808 and 247, respectively. Because patients with an indication for vericiguat only represent a small proportion of the HFrEF population, the number of pregnancies that may be potentially exposed to vericiguat is expected to be even smaller.

The prescribing information for vericiguat will describe the potential serious risk of embryo-fetal toxicity with a boxed warning, which states: “Females of reproductive potential: Exclude pregnancy before the start of treatment, (b) (4) (b) (4). To prevent pregnancy, females of reproductive potential must use effective forms of contraception during treatment and for one month after stopping treatment. Do not administer Verquvo to a pregnant female because it (b) (4) cause fetal harm [see Dosage and Administration (2.X), Warnings and Precautions (5.X), and Use in Specific Populations (8.3)].”

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.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an “X” in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	

Identify unexpected serious risk when available data indicate potential for serious risk | X |

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
☐ No approved indication, but practitioners may use product off-label in pregnant women
☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† *If checked, please complete Error! Reference source not found..*

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☐ Electronic database study without chart review
☒ Other, please specify: Single arm pregnancy surveillance study

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☒ Outcomes
☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes

The broad-based surveillance may include pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on infants in exposed pregnancies. The ARIA system lacks access to detailed narratives. Given that the study for broad-based pregnancy outcomes being considered is descriptive, without sample size requirements, and without a comparison group, having detailed narratives is necessary to identify and validate outcomes and to assess exposure and outcome temporality. Only a subset of pregnancy and birth outcomes have validated algorithms the ARIA system.

Analytical tools

ARIA analytic tools are not sufficient to assess the regulatory question of interest 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 were not assessed. Because broad-based signal detection is not currently available, other parameters have not been assessed.

2.5. Please include the proposed PMR language in the approval letter.

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.

In order to ensure capture of the key data elements related to vericiguat exposure during pregnancy, we refer you to the draft FDA Guidance for Industry: “Postapproval Pregnancy Safety Studies”.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YAN LI
11/24/2020 01:52:56 PM

MARIE N BRADLEY
11/24/2020 01:55:39 PM

EFE EWORUKE
11/24/2020 02:06:07 PM

MICHAEL D NGUYEN
11/24/2020 02:07:46 PM

ROBERT BALL
11/24/2020 03:07:31 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 23, 2020
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214377
Product Name and Strength:	Verquvo (vericiguat) tablets, 2.5 mg, 5 mg and 10 mg
Applicant/Sponsor Name:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
OSE RCM #:	2020-1052-1
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on November 6, 2020 for Verquvo. We reviewed the revised container labels and carton labeling for Verquvo (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Straka M. Label and Labeling Review for Verquvo (NDA 214377). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Oct 22. RCM No.: 2020-1052.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MAXIMILIAN STRAKA
11/23/2020 10:44:04 AM

HINA S MEHTA
11/24/2020 09:59:57 AM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: November 4, 2020

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst
Division of Cardiology and Nephrology

To: Alexis Childers
DCN

Subject: QT Consult to NDA 214377 (SDN 024)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 9/28/2020 regarding questions from the Division concerning nonclinical assessment and additional ECG analysis of VICTORIA. We reviewed the following materials:

- Draft ion channel study protocol (link)
- Final ion channel study protocol (NDA 214377 / eCTD 0030; link);
- Summary of nonclinical (NDA 214377 / eCTD 0024; link);
- Nonclinical study report PH-41772 (NDA 214377 / eCTD 0024; link);
- Nonclinical study report PH-41774 (NDA 214377 / eCTD 0024; link); and
- Previous IRT review(s) for NDA 214377 dated 08/25/2020 in DARRTS.

1 Responses for the Division

The sponsor submitted a summary of nonclinical experiments to characterize the effects of vericiguat and M1 on multiple ion currents. The experimental design of the ion channel study protocols differs from the recommendations that we generally provide to sponsors (e.g., the voltage protocols were different, and the experiments were (b) (4)). The results of these experiments do therefore not alter our previous conclusions about the potential for QT prolongation for vericiguat as the results of these experiments do not support an integrated risk assessment per the revised ICH S7B Q&As 1.1-1.2. It is also unclear if the negative finding in these experiments supports that the characterization of the "worst case

scenarios" as requested by the division, particularly because the experiments did not include concentration verification. To address these limitations, the sponsor submitted a new ion channel study protocol. We reviewed the protocol and provided our comments, which were incorporated in the final protocol submitted by the sponsor.

We also conducted additional outlier analysis of the ECG data collected in the VICTORIA study focusing on QTcF and QRS for patients in the upper 4th quartile of NT-proBNP. The results of this analysis do not suggest any imbalance for patients without a device for QTcF and QRS.

2 Internal Comments for the Division

Not applicable.

3 BACKGROUND

3.1 Sponsor's position related to the question

Please note that in response to FDA's request from the Mid-Cycle meeting, we subsequently completed evaluation of the potential effects of vericiguat and its M1 N-glucuronide metabolite on the following human cardiac ion channels (b) (4): human Ether-à-go-go-Related Gene (hERG; also known as hKv11.1), hNav1.5, hKv4.3/hKChIP2.2 (hIto), hKv7.1/hKCNE1 (hIKs), and hCav1.2. These experiments were conducted using (b) (4) No clinically relevant effects were observed at maximum concentrations tested in excess of approximately (b) (4) times the human Cmax (unbound) levels, 18 nM for vericiguat or 43 nM for M1, at the maximum recommended human dose (MRHD) of 10 mg.

Given such margins, as well as the observations from Crumb et al (2016) and Kramer et al (2013) that IC50's for a wide array of compounds do not differ substantially when assayed using standard vs CiPA protocols, **it is our perspective that additional investigations applying the CiPA protocol would not further inform on a pro-arrhythmic risk. Does FDA agree?**

If FDA does not agree, we would appreciate a teleconference meeting with FDA at earliest possible convenience (preferably next week) to discuss the ion channel data package given the discussion at the Mid-Cycle Review meeting and recent FDA email communication. A short turnaround in FDA's response would be greatly appreciated, as we are in the process of preparing a detailed report on the ion channel data, targeted for submission to FDA by early next week.

3.2 Nonclinical Cardiac Safety

Effects of vericiguat and its M1 N-glucuronide metabolite were evaluated on the following human cardiac ion channels in non-GLP assays (b) (4): human Etherà-go-go-Related Gene (hKv11.1 (hERG)), hNav1.5, hKv4.3/hKChIP2.2 (hIto), hKv7.1/hKCNE1 (hIKs), and hCav1.2. The voltage protocols, internal and external solutions, and positive controls utilized were industry standard; details are provided in the accompanying reports (PH-41772) (PH-41774). A summary of the results is provided below in Table 1 and 1. Importantly, no clinically relevant effects were observed with either vericiguat or M1 at exposure multiples in

excess of approximately [redacted] times the human Cmax (unbound) of 18 nM for vericiguat or 43 nM for M1, at the maximum recommended human dose (MRHD) of 10 mg.

Table 1: Summary of cardiac ion channel data with vericiguat

Ion Channel	Inhibition@ 10 μM	IC50 (μM)	Exposure Multiple
hERG K+ Outward tail	[redacted]		
hERG K+ Inward tail			
hNav1.5			
hCav1.2			
hKvLQT1			
hKv4.3			
Exposure multiples calculated based on human clinical Cmax (unbound) of 18 nM, compared with the IC50 or highest concentration tested for each channel.			

Table 2: Summary of cardiac ion channel data with M1, an N-glucuronide metabolite of vericiguat

Ion Channel	Inhibition@ 10 μM	IC50 (μM)	Exposure Multiple
hERG K+ Outward tail	[redacted]		
hERG K+ Inward tail			
hNav1.5			
hCav1.2			
hKvLQT1			
hKv4.3			
Exposure multiples calculated based on human clinical Cmax (unbound) of 43 nM, compared with the IC50 or highest concentration tested for each channel.			

Reviewer's assessment: *The sponsor evaluated the effects of vericiguat (report ID: PH-41772) and the M1 metabolite (report ID: PH-41774) on cardiac ion channels including hERG, Nav1.5, Cav1.2, KvLQT1 and Kv4.3 channels. These current assays were* [redacted] *. The sponsor's voltage protocols for hERG, Nav1.5 and Cav1.5 assays are different from the recommended voltage protocols by the FDA (link).* [redacted] *The consequences of these assay protocol and process deviations on drug pharmacology are unclear.*

[redacted]

In summary, the new nonclinical cardiac ion channel assays deviated from the best practice recommended per the new ICH S7B Q&As 2.1 (link) and therefore these data cannot be included in an integrated risk assessment.

Following a teleconference with FDA on Oct 7, 2020 regarding the need of performing additional ion channel studies using the Comprehensive in vitro Proarrhythmia Assay (CiPA) protocol, the sponsor submitted a draft protocol (link) for assessing the effects of vericiguat and its M1 metabolite on hERG, KvLQT1/mink (IKs), Nav1.5 and Cav1.2 currents using the recommended voltage protocols by FDA. We reviewed the proposed protocol for ion channel studies and added our comments/edits. We propose not to conduct experiments of Cav1.2 and late Nav1.5 assays. We have provided recommendations for hERG, Nav1.5 and KvLQT1/mink experiments, including changes to ensure that the experiments reflect "worst case scenario", i.e. depolarized holding potential (at -70 mV) to mimic depolarized myocyte membrane potential and elevated heart rate in patients with heart failure. In addition, we also provided recommendations for internal/external solutions, temperature control, recording stability and drug concentration verification to ensure that the experiments follow the in vitro assay best practices per the new ICH S7B Q&As.

The sponsor accepted our recommendations/suggestions and added a few minor comments on the final study protocol (link) on Oct 22, 2020. In the IKs assay, the sponsor added a comment: "if a pacing rate of 1Hz is associated with marked current rundown, then a slower pacing rate (e.g.0.5Hz) will be used". In the Nav1.5 assay, the sponsor had the following comment: "If a holding potential of -70mV reduces current amplitude significantly, then a less depolarized holding potential (e.g. -80mV) will be used". Those two comments are reasonable, and those minor changes are not expected to have an impact on our ability to conclude absence of an effect.

3.3 Clinical Cardiac Safety

ECG outlier analysis was conducted for patients in VICTORIA in the highest NT-proBNP quartile, which show no increase in QTcF (Table 1) or QRS (Table 2) outliers for vericiguat patients vs placebo patients without a device.

Table 1: QTcF outliers for VICTORIA patients in the highest NT-proBNP quartile

Treatment	Device	Total (N)		Value <= 450 msec		450 msec < Value <= 480 msec		480 msec < Value <= 500 msec		Value > 500 msec & < 60 msec		Value > 500 msec & >= 60 msec	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Vericiguat	Biventricular Pacemaker Only	34	67	2 (5.9%)	4 (6.0%)	3 (8.8%)	14 (20.9%)	7 (20.6%)	16 (23.9%)	20 (58.8%)	31 (46.3%)	2 (5.9%)	2 (3.0%)
	ICD Only	93	185	28 (30.1%)	60 (32.4%)	22 (23.7%)	54 (29.2%)	13 (14.0%)	31 (16.8%)	22 (23.7%)	30 (16.2%)	8 (8.6%)	10 (5.4%)
	ICD and Biventricular Pacemaker	46	85	3 (6.5%)	11 (12.9%)	8 (17.4%)	17 (20.0%)	8 (17.4%)	15 (17.6%)	19 (41.3%)	31 (36.5%)	8 (17.4%)	11 (12.9%)
	No Device	320	568	141 (44.1%)	312 (54.9%)	95 (29.7%)	148 (26.1%)	44 (13.8%)	58 (10.2%)	30 (9.4%)	40 (7.0%)	10 (3.1%)	10 (1.8%)
Placebo	Biventricular Pacemaker Only	28	52	5 (17.9%)	11 (21.2%)	5 (17.9%)	8 (15.4%)	6 (21.4%)	11 (21.2%)	11 (39.3%)	21 (40.4%)	1 (3.6%)	1 (1.9%)
	ICD Only	80	158	24 (30.0%)	60 (38.0%)	23 (28.7%)	45 (28.5%)	13 (16.2%)	30 (19.0%)	14 (17.5%)	16 (10.1%)	6 (7.5%)	7 (4.4%)
	ICD and Biventricular Pacemaker	40	73	4 (10.0%)	11 (15.1%)	6 (15.0%)	15 (20.5%)	10 (25.0%)	18 (24.7%)	17 (42.5%)	26 (35.6%)	3 (7.5%)	3 (4.1%)
	No Device	313	547	134 (42.8%)	293 (53.6%)	102 (32.6%)	154 (28.2%)	34 (10.9%)	48 (8.8%)	33 (10.5%)	42 (7.7%)	10 (3.2%)	10 (1.8%)

Table 2: QRS outliers for VICTORIA patients in the highest NT-proBNP quartile

Treatment	Device	Total (N)		Value <= 120 msec		Value > 120 msec & < 25%		Value > 120 msec & >= 25%	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Vericiguat	Biventricular Pacemaker Only	34	67	2 (5.9%)	5 (7.5%)	28 (82.4%)	57 (85.1%)	4 (11.8%)	5 (7.5%)
	ICD Only	93	188	35 (37.6%)	83 (44.1%)	46 (49.5%)	85 (45.2%)	12 (12.9%)	20 (10.6%)
	ICD and Biventricular Pacemaker	46	86	7 (15.2%)	17 (19.8%)	33 (71.7%)	62 (72.1%)	6 (13.0%)	7 (8.1%)
	No Device	323	571	195 (60.4%)	381 (66.7%)	114 (35.3%)	175 (30.6%)	14 (4.3%)	15 (2.6%)
Placebo	Biventricular Pacemaker Only	28	52	4 (14.3%)	10 (19.2%)	22 (78.6%)	39 (75.0%)	2 (7.1%)	3 (5.8%)
	ICD Only	82	162	32 (39.0%)	84 (51.9%)	40 (48.8%)	68 (42.0%)	10 (12.2%)	10 (6.2%)
	ICD and Biventricular Pacemaker	41	72	2 (4.9%)	6 (8.3%)	33 (80.5%)	60 (83.3%)	6 (14.6%)	6 (8.3%)
	No Device	318	558	183 (57.5%)	359 (64.3%)	119 (37.4%)	180 (32.3%)	16 (5.0%)	19 (3.4%)

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LARS JOHANNESEN
11/04/2020 08:58:38 AM

DONGLIN GUO
11/04/2020 10:21:53 AM

CHRISTINE E GARNETT
11/04/2020 10:23:00 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 22, 2020
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214377
Product Name, Dosage Form, and Strength:	Verquvo (vericiguat) tablets, 2.5 mg, 5 mg and 10 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
FDA Received Date:	May 20, 2020 and October 13, 2020
OSE RCM #:	2020-1052
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. submitted NDA 214377 Verquvo (vericiguat) tablets on May 20, 2020. Verquvo is being proposed 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 therapies. We reviewed the proposed container labels, carton labeling, professional samples, Prescribing Information (PI), and Patient Information for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Merck submitted a 505(b)(1) application to obtain marketing approval for Verquvo (vericiguat) tablets. Verquvo is being proposed in 2.5 mg, 5 mg, and 10 mg tablet strengths. We note the initial starting dose is 2.5 mg once daily followed by increase dose to 5 mg once daily after 2 weeks. The target dose if tolerated is 10 mg once daily with food. In response to an Information Request sent by the Office of Pharmaceutical Quality, Merck sent an updated representation on October 13, 2020 of the intent to market blister carton and blister-card with the location of the drug product lot or control number. We defer to Office of Pharmaceutical Quality (OPQ) on the appropriateness of statement “Package not child resistant” on the blister carton labeling. If deemed necessary we recommend relocating this statement to the back panel of the blister carton labeling.

We performed a risk assessment of the proposed bottle container labels, bottle carton labeling, blister card labels, blister card carton labeling, professional sample labeling, Prescribing Information (PI) and Patient Information for Verquvo (vericiguat) tablets to determine whether there are significant concerns in terms of safety related to preventable medication errors. For the

prescribing information we note lack of clarity on route of administration and lack of clarity on how supplied.

We note that the "Rx Only" statement competes in prominence with the other important information on the principal display panel. We note the lack of the placeholder for the 2D data matrix. We note that the HUD Blister-card mockup shows the Expiry depicted in a YYYYMMMDD format, however the expiration date format is not defined on the bottle container label or blister carton labeling. We provide recommendations for the PI for the Division in Section 4.1 and for the carton and container labeling for Merck in Section 4.2 below. We find the patient information sheet acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed carton labeling, professional samples, bottle container labels, and PI can be improved from a medication error perspective. We provide recommendations for the PI for the Division in Section 4.1 and for the carton and container labeling for Merck in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY

A. Highlights and Full Prescribing Information
    1. We recommend including the route of administration as part of the statement regarding recommended dosage.

B. Full Prescribing Information, How Supplied
    1. We recommend removing (b) (4) as this description is not necessary. In addition, we recommend revising the description of the blister cartons to "carton of 100 tablets (10 blister cards of 10 tablets each)" for increased clarity.

4.2 RECOMMENDATIONS FOR MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Bottle and Sample Container labels & Blister Carton Labeling)
    1. We recommend revising the storage information for consistency as currently presented it includes "to", "-", and "and" when describing storage requirements. Revise to "20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (between 59°F to 86°F). See USP for controlled room temperature.".
    2. Consider decreasing the prominence of the statement "Rx Only" by debolding it as this information appears more prominent than the established name on the principal display panel.
    3. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical

characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.

B. Bottle Container Labels

a. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[a] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. If you determine that the product identifier requirements apply to your product's labeling, we request you add a placeholder for the human-readable and machine-readable (2D data matrix barcode) product identifier to the container label.

b. We recommend revising the second bullet point in the "Additional Dosage Information" section to read: "Take your dose at the same time each day with food." for clarity.

C. Blister Carton Labeling

1. As currently presented, it is not immediately clear on the labeling that the designated strength (i.e., 5 mg) is per tablet. Failure to express the product strength as 5 milligram per tablet may lead to wrong dose errors. Revise the strength statement "5 mg" to state "5 mg per tablet" to make it clear that the designated strength is per unit so there is no confusion as to how much product is contained in a single unit as compared to the total contents of the entire carton labeling

2. We recommend revising the net quantity statement for clarity. Revise to "100 tablets (10 blister cards x 10 tablets each)".

---

[a] The draft guidance is available from: https://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Verquvo received on May 20, 2020 from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc..

Table 2. Relevant Product Information for Verquvo	
Initial Approval Date	N/A
Active Ingredient	vericiguat
Indication	Verquvo is 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 therapies.
Route of Administration	oral
Dosage Form	tablets
Strength	2.5 mg, 5 mg and 10 mg
Dose and Frequency	The recommended starting dose of Verquvo is 2.5 mg once daily, taken with food. The dose should be doubled approximately every 2 weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient.
How Supplied	Verquvo (vericiguat) tablets are available in the strengths listed below: • 2.5 mg film-coated tablets are round, biconvex, white with "2.5" debossed on one side and "VC" on the other side. They are supplied as follows: o NDC 0006-5028-01 (b) (4) bottles of 14 o NDC 0006-5028-02 bottles of 30 o NDC 0006-5028-04 blister packages of 100 (10 strips of 10 tablets) • 5 mg film-coated tablets are round, biconvex, brown-red with "5" debossed on one side and "VC" on the other side. They are supplied as follows: o NDC 0006-5029-01 (b) (4) bottles of 14 o NDC 0006-5029-02 bottles of 30 o NDC 0006-5029-04 blister packages of 100 (10 strips of 10 tablets) • 10 mg film-coated tablets are round, biconvex, yellow-orange with "10" debossed on one side and "VC" on the other side. They are supplied as follows: o NDC 0006-5030-01 (b) (4) bottles of 30 o NDC 0006-5030-02 bottles of 90 o NDC 0006-5030-04 blister packages of 100 (10 strips of 10 tablets)
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (between 59°F and 86°F). See USP for Controlled Room Temperature.
Container Closure	The commercial packages for Vericiguat coated tablets will be packaged in high density polyethylene (HDPE) bottles and closures with heat induction seal liner, and in (b) (4) blister and lidding.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 9, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Verquvo, vericiguat and NDA 214377. Our search did not identify any relevant reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Verquvo labels and labeling submitted by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc..

- Container label received on May 20, 2020.
- "PEEL HERE" Additional Dosage Information received on May 20, 2020.
- Hospital Unit-Dose (HUD) Carton Labeling received on May 20, 2020.
- HUD Blister Card labels received on May 20, 2020.
- HUD Carton and Blister Card Label Mock-Up received on October 13, 2020.
- Professional Sample Container Labeling received on May 20, 2020.
- Prescribing Information (Image not shown) received on May 20, 2020, available from \\CDSESUB1\evsprod\nda214377\0001\m1\us\01-crt-uspi-mk1242-t-original.doc
- Patient Information (Image not shown) received on May 20, 2020, available from \\CDSESUB1\evsprod\nda214377\0001\m1\us\01-crt-usppi-mk1242-t-original.doc

G.2 Label and Labeling Images

Container Labels

(b) (4)

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MAXIMILIAN STRAKA
10/22/2020 10:20:53 AM

HINA S MEHTA
10/22/2020 02:25:02 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: October 16, 2020 **Date consulted:** August 28, 2020

From: Carrie Ceresa, Pharm D., MPH, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: The Division of Cardiology and Nephrology (DCN)

Drug: Verquvo (vericiguat) tablets, for oral use

NDA: 214-377 (IND (b) (4))

Applicant: Merck Sharp and Dome

Subject: Pregnancy and Lactation Labeling Recommendations and Formatting

Proposed Indication: 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 therapies.

Materials Reviewed:

- May 20, 2020, Original New Drug Application (NDA 214377) for vericiguat tablets

- October 12, 2017, DPMH review for ADEMPAS (riociguat), NDA 204819, Cathy Roca, M.D., Medical Officer, DARRTS Reference ID 4164696[1]
- June 24, 2013, DPMH review of riociguat, NDA 204819, Tammie Howard, RN, MSN, DARRTS Reference ID 3330766[1]
- October 17, 2013, DPMH review of riociguat, NDA 204819, Tammie Howard, RN, MSN, DARRTS Reference ID 3391829[1]

Consult Question: "The labeling for vericiguat will include a description of embryo-fetal effects and risk mitigation similar to that for riociguat. Because of the differences in patient population and prescriber practices, vericiguat will not have a REMS. Please work with the review team on labeling and appropriate collection of postmarketing data (via PMR/ PMC) to provide information on exposure during pregnancy."

INTRODUCTION AND BACKGROUND

On May 20, 2020, Merck submitted an Original New Drug Application 214377 for Verquvo (vericiguat) tablets 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 therapies. The Division of Cardiology and Nephrology (DCN) consulted the Division of Pediatric and Maternal Health (DPMH) on August 28, 2020, to assist with the Pregnancy and Lactation subsections of labeling.

Table 1: Vericiguat Drug Characteristics[2]

Drug Class	Soluble guanylate cyclase (sGC)
Mechanism of Action	Myocardial and vascular dysfunction is derived from a deficiency in sGC-derived cGMP. Proposed mechanism is thought that vericiguat restores this deficiency in the signaling pathway by directly stimulating sGC synergistically with nitric oxide which augments the levels of intracellular cGMP which may improve both myocardial and vascular function
Dose and Administration	Starting dose of 2.5 mg once daily with food doubled every two weeks to reach the maintenance dose of 10 mg daily (can also be crushed)
Molecular Weight	426.39 g/mol
Protein Binding	High protein binding 98% serum albumin primary binding component
Terminal Half-Life	(b) (4) 30 hours in HF patients
Bioavailability	93% when taken with food
Warnings and Precautions	(b) (4)
Adverse Reactions	

[1] The labeling review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.
[2] Applicant's proposed vericiguat labeling.

REVIEW
PREGNANCY

Heart Failure and Pregnancy

- Approximately 6.2 million adults over the age of 20 in the U.S. have heart failure with equal numbers between men and women. At age 40, the lifetime risk of developing heart failure for both men and women is 1 in 5.[3,4]
- Significant hemodynamic changes occur during pregnancy such as 30 to 50% increases in cardiac output and blood volume.[5,6] (Refer to Table 1 in Appendix A for cardiovascular changes in normal pregnancy)
- Decompensation can occur in women with a history of heart failure or other cardiovascular disorders during pregnancy or the peripartum period.[5]
- Peripartum cardiomyopathy is cardiac failure with left ventricular ejection fraction of < 45% occurring in the last month of pregnancy or within five months of delivery however it is a rare condition occurring in approximately 1 in 3,000 to 15,000 pregnancies.[7]
- Management of the treatment of HF during pregnancy is challenging as many of the first line agents (such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers and angiotensin receptor-neprilysin inhibitors) used to treat HF in non-pregnant women are contraindicated during pregnancy.[5]
- The risk of HF during pregnancy is increased in women with cardiomyopathy, mitral stenosis, aortic stenosis and severe mitral or aortic regurgitation.[5]
    - Maternal mortality is higher during pregnancy in women with dilated cardiomyopathy with left ventricular ejection fraction < 20%. According to the American College of Obstetrics and Gynecology (ACOG), in the United States disease and dysfunction of the heart is the leading cause of death in pregnant women and women in the postpartum period which accounts for approximately 4.23 deaths per 100,000 live births.[8]
- Chronic heart failure treatment in pregnant women can be treated with the use of diuretics, beta blockers, hydralazine plus nitrate and digoxin.
- Acute heart failure treatment in pregnant women with severe decompensated HF with stable or elevated blood pressure is treated with intravenous vasodilator therapy with nitroglycerin along with hemodynamic and fetal monitoring. Acute decompensated HR is managed similarly to nonpregnant patients with decompensated HFrEF. See Appendix A for ACOG review of cardiac medications and pregnancy and lactation recommendations.

---

[3]https://www.cdc.gov/heartdisease/heart_failure.htm. Accessed October 9, 2020.
[4] Bozkurt B and Khalaf S. Heart Failure in Women. Methodist DeBakey Cardiovascular Journal 2017; 13(4): 216-223.
[5] DeCara J, R Lang & M Foley. Management of heart failure during pregnancy. In: UpToDate, Colucci W et al. (Eds), UpToDate, Waltham, MA. (accessed on September 12, 2020)
[6] Heart conditions and pregnancy: Know the risks. Mayo clinic. https://www.mayoclinic.org/healthy-lifestyle/pregnancy-week-by-week/in-depth/pregnancy/art-20045977 (accessed on September 12, 2020)
[7] Thorne SA. Pregnancy in heart disease. Heart. 2004 Apr: 90(4):450-456.
[8] Pregnancy and Heart Disease. American College of Obstetrics and Gynecology (ACOG). Practice Bulletin number 212, May 2019. https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2019/05/pregnancy-and-heart-disease (accessed on September 12, 2020)

Nonclinical Experience

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. In pre- and postnatal studies, vericiguat administered orally to rats from gestation through lactation displayed pharmacodynamic-mediated maternal toxicity at approximately ≥ 9 times the MRHD resulting in decreased pup body weight gain at ≥ 21 times the MHRD and pup mortality at 49 times the MRHD. Genotoxicity was not demonstrated. Refer to Pharmacology/Toxicology primary review and addendum by Elizabeth Hausner, Ph.D., for a final review of all non-clinical reproductive studies, DARRTS.

Reviewer comment: The Pharmacology/Toxicology review addendum was not complete at the time the DPMH review was finalized and the data above are subject to change upon final review.

Vericiguat clinical trials

Subjects were excluded from phase 2 b and phase 3 clinical trials if they were pregnant or breastfeeding, or planning to become pregnant or breastfeeding. In addition, no pregnancies were reported in any of the trials in pregnant women or in the female partners of subjects exposed to vericiguat. The applicant recommends that vericiguat is not used during pregnancy or in females of reproductive potential due to the potential for adverse hemodynamic effects in pregnant women based on the drug's mechanism of action.

Review of Literature

The applicant did not provide a review of published literature with regard to vericiguat exposure during pregnancy; however, DPMH conducted a search of published literature using PubMed and Embase, and no data were found. Vericiguat is not referenced in Micromedex[9] or *Drugs in Pregnancy and Lactation* by Briggs and Freeman.[10] The reader is also referred to the DPMH review for riociguat, another soluble guanylate cyclase (sGC).[11]

Reviewer comment:
The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

[9] Vericiguat. (b) (4) Micromedex.
[10] Briggs, GG and Freeman, R., Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk Online version: http://ovidsp.tx.ovid.com/sp-3.31.1b/ovidweb.cgi.
[11] October 12, 2017, DPMH review for ADEMPAS (riociguat), NDA 204819, Cathy Roca, M.D., Medical Officer, DARRTS Reference ID 4164696.

LACTATION

Nonclinical Experience

Milk samples in pre- and postnatal development studies were not analyzed for secretion or concentration of vericiguat. However, in a radiolabeled distribution study in pregnant female rats, high exposure of drug was found in the mammary gland of lactating rats suggesting presence of the vericiguat or its metabolites in rat milk. Refer to Pharmacology/Toxicology primary review and addendum by Elizabeth Hausner, Ph.D., for a final review of all non-clinical reproductive studies, DARRTS.

Reviewer comment: The Pharmacology/Toxicology review addendum was not complete at the time the DPMH review was finalized and the data above are subject to change upon final review.

Review of Literature

The applicant did not provide a review of published literature with regard to vericiguat exposure during lactation; however, DPMH conducted a search of published literature using PubMed and Embase and no data were found. Vericiguat is not referenced in in LactMed,[12] *Medication and Mothers Milk,*[13] or *Drugs in Pregnancy and Lactation* by Briggs and Freeman.[10,11]

Reviewer comment:
The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

There were no effects on fertility, mating performance or early embryonic development when vericiguat was administered to rats at 66 times the MRHD. At 12 times the MRHD a decrease in average number of estrus cycles was reported in female rats. Refer to Pharmacology/Toxicology primary review and addendum by Elizabeth Hausner, Ph.D., for a final review of all non-clinical reproductive studies, DARRTS.

Reviewer comment: The Pharmacology/Toxicology review addendum was not complete at the time the DPMH review was finalized and the data above are subject to change upon final review.

Review of Literature

The applicant did not provide a review of published literature with regard to vericiguat exposure and effects on fertility; however, DPMH conducted a search of published literature using PubMed and Embase, and no data were found.

Reviewer comment:
The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

[12] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
[13] Hale, Thomas (2017). Medications and Mother's Milk. Amarillo, Texas. Springer Publishing Company LLC.

DISCUSSION AND CONCLUSIONS

Pregnancy

Overall, there are no human data with regard to vericiguat exposure during pregnancy. 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 ≥ (b) (4) times, respectively, the human exposure at the MRHD which resulted in late spontaneous abortions and resorptions in rabbits.

Although there are no data on the use of vericiguat exposure during pregnancy, there is still the possibility of unintended pregnancies in females of reproductive potential who are exposed to vericiguat to treat heart failure. In addition, the proposed indication for vericiguat is 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%. Due to the effects observed in non-clinical studies vericiguat will be contraindicated in pregnancy; therefore, DPMH does not believe a pregnancy registry would be feasible in this population. DPMH recommends issuing a postmarketing requirement (PMR) for a Single-Arm Pregnancy Safety Study. The goal of a post-approval pregnancy safety study is to provide clinically relevant human safety data that can inform healthcare providers treating or counseling patients who are pregnant or anticipating pregnancy about the safety of drugs and biological products through inclusion of information in a product's labeling. The reader is referred to the FDA Draft Guidance for Industry Postapproval Pregnancy Safety Studies: Considerations for Study Design, published May 2019, for further details.

Lactation

There are no data on the presence of vericiguat in human milk, the effects on the breastfed infant/child or the effects on milk production. Milk samples in pre- and postnatal development studies were not analyzed for secretion or concentration of vericiguat. However, in a radiolabeled distribution study in pregnant female rats, high exposure of drug was found in the mammary gland of lactating rats suggesting presence of the vericiguat or it's metabolites in rat milk. Chemical properties of vericiguat, including the molecular weight of 426.39 g/mol, oral bioavailability 93% when taken with food and half-life of 30 hours in HF patients, suggest that vericiguat may be present in breast milk and could accumulate. Given the potential for toxicity to the breastfed infant such as hypotension, females should be advised not to breastfeed while taking vericiguat.

Females and Males of Reproductive Potential

There is no evidence suggesting vericiguat adversely affects female fertility. There are no reported drug to drug interaction (DDI) between vericiguat and hormonal birth control. There were no effects on fertility, mating performance or early embryonic development when vericiguat was administered to rats at 66 times the MRHD. Vericiguat has the potential to cause embryofetal toxicity based on the drug's mechanism of action and results from animal reproduction studies; therefore, subsection 8.3 Females and Males of Reproductive Potential will contain information about pregnancy testing and contraception.

POSTMARKETING REQUIREMENT (PMR) RECOMMENDATIONS

1. 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.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **Do not administer Verquvo to a pregnant female because it (b) (4) cause fetal harm. (4,5.3,8.1)**
- **Females of reproductive potential: Exclude pregnancy before start of treatment (b) (4) (b) (4). To prevent pregnancy, females of reproductive potential must use effective forms of contraception during treatment and for one month after treatment discontinuation (2.2, (b) (4) 5.3, 8.3)**

---------- CONTRAINDICATIONS ----------

- Pregnancy (4)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Breastfeeding not recommended (8.2)

FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Do not administer Verquvo to a pregnant female because it (b) (4) cause fetal harm *[see (b) (4) Warnings and Precautions (5.3) and Use in Specific Populations (8.1)]*.

Females of reproductive potential: Exclude pregnancy before the start of (b) (4) (b) (4) treatment. To prevent pregnancy, females of reproductive potential must use effective forms of contraception during treatment and for one month after stopping treatment *[see Dosage and Administration (2.2), Warnings and Precautions (5.3), and Use in Specific Populations (8.3)]*.

2 Dosage and Administration

2.X Pregnancy Testing in Females of Reproductive Potential

Obtain a pregnancy test in females of reproductive potential prior to initiating treatment (b) (4) (b) (4) with Verquvo *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.3)]*.

4 Contraindications

Verquvo is contraindicated in pregnancy *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)]*.

5 Warning and Precautions

5.3 Embryo-fetal Toxicity

Based on data from animal reproduction studies, Verquvo (b) (4) cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential of the potential risk to a fetus. Obtain a pregnancy test before the start of (b) (4) (b) (4). Advise females of reproductive potential to use effective contraception during treatment with Verquvo and for at least one month after the final dose *[see Dosage and Administration (2.2) and Use in Specific Populations (8.1, 8.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on data from animal reproduction studies, Verquvo (b) (4) cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy *[see Contraindications (4)]*. There are no available data with Verquvo use in pregnant women.

[Refer to Pharmacology/Toxicology review and final NDA labeling for animal data risk summary language]

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.

[redacted] If a patient becomes pregnant while receiving Verquvo, healthcare providers should report Verquvo exposure by calling xxx-xxx-xxxx [redacted]

Data
Animal Data
[Refer to Pharmacology/Toxicology review and final NDA labeling for animal data language]

8.2 Lactation
Risk Summary
There are no data on the presence of vericiguat in human milk, the effects on the breastfed infant, or the effects on milk production. Vericiguat is present in the [redacted] of lactating rats and it is likely that vericiguat or its metabolites are present in human milk. Because of the potential for serious adverse reactions, [redacted] in breastfed infants from Verquvo, advise women not to breastfeed during treatment with Verquvo.

8.3 Females and Males of Reproductive Potential
Pregnancy Testing
Verify the pregnancy status in females of reproductive potential prior to initiating Verquvo, [redacted] *[see Dosage and Administration (2.2) and Use in Specific Populations (8.1)]*.

Contraception
Females
Verquvo [redacted] cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment and for one month after the final dose. [redacted]

17 PATIENT COUNSELING INFORMATION
Embryo-fetal Toxicity
Advise pregnant women and females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy. Advise females of reproductive potential to use effective contraception during treatment with Verquvo and for one month after the final dose *[see Contraindication (4), Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.3)]*.

Pregnancy
Advise women who are exposed to Verquvo during pregnancy [redacted] to report their pregnancy to [redacted] *[see Use in Specific Populations (8.1)]*.

Lactation
Advise women not to breastfeed during treatment with Verquvo *[see Use in Specific Populations (8.2)]*.

Appendix A.

Table 1. Cardiovascular Changes in a Normal Pregnancy (copied from ACOG practice bulletin Number 212, corresponds to Table 1, page e322)[5]

	First Trimester	Second Trimester	Third Trimester	Stage 1 Labor	Stage 2 Labor	Early Postpartum	3–6 months Postpartum
Cardiac output	↑5–10%	↑↑35–45%		↑30%	↑↑50%	↑↑↑60–80% immediately, then rapidly decreases within the first hour	Return to prepregnancy values
Heart rate	↑3–5%	↑10–15%	↑15–20%	During uterine contractions: ↑40–50%		↓5–10% within 24 hours; continues to decrease throughout the first 6 weeks	Return to prepregnancy values
Blood pressure	↓10%	↓5%	↑5%	During uterine contractions: ↑SBP 15–25% ↑DBP 10–15%		↓SBP 5–10% within 48 hours; may increase again between days 3–6 due to fluid shifts	Return to prepregnancy values
Plasma volume	↑	↑↑40–50%		↑	↑↑	↑↑↑500 mL due to autotransfusion	Return to prepregnancy values

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure.

*Hemodynamic changes that occur during pregnancy, labor, and postpartum (compared with prepregnancy) should be understood to identify early interventions (such as blood pressure control and diuresis) that may be needed to prevent clinical deterioration in a woman with cardiovascular disease.

Data from Kuhn JC, Falk RS, Langesaeter E. Haemodynamic changes during labour: continuous minimally invasive monitoring in 20 healthy parturients. Int J Obstet Anesth 2017;31:74–83; Ouzounian JG, Elkayam U. Physiologic changes during normal pregnancy and delivery. Cardiol Clin 2012;30:317–29; Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. Circulation 2014;130:1003–8; Shen M, Tan H, Zhou S, Smith GN, Walker MC, Wen SW. Trajectory of blood pressure change during pregnancy and the role of pre-gravid blood pressure: a functional data analysis approach. Sci Rep 2017;7:6227; Sohnchen N, Melzer K, Tejada BM, Jastrow-Meyer N, Othenin-Girard V, Irion O, et al. Maternal heart rate changes during labour. Eur J Obstet Gynecol Reprod Biol 2011;158:173–8; and Walters BN, Walters T. Hypertension in the puerperium [letter]. Lancet 1987;2:330.

Table 2. Cardiac Medications with Potential Pregnancy and Lactation Influence (copied from ACOG practice bulletin Number 212, corresponds to Table 5, page e328 and e329)[5]

Drug	Teratogenic	Fetal Effects	Breastfeeding
Inotropic Agents			
Dopamine	No	No adverse fetal effects	Probably compatible, may inhibit prolactin release
Dobutamine	No	No adverse fetal effects	Probably compatible
Epinephrine	No	No adverse fetal effects when used acutely	Probably compatible
Vasodilators			
Nitroprusside	No	Potential for fetal cyanide toxicity with high doses	Possibly hazardous
Hydralazine	No	Relatively safe for the fetus	Probably compatible
Nitroglycerin	No	No adverse fetal effects Observe for risks of methemoglobinemia	Possibly hazardous
Ephedrine sulfate	No	No adverse fetal effects when used acutely	Possibly hazardous with chronic use
Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers			
	Yes	Contraindicated Associated with fetal renal failure, growth restriction, malformations and death	Probably compatible No published information
Beta-blockers			
Propranolol	No	May increase risk of growth restriction	Probably compatible
Labetalol	No	No adverse fetal effects	Probably compatible
Atenolol	No	May increase risk of growth restriction	Probably compatible Limited information
Metoprolol	No	May increase risk of growth restriction	Probably compatible
Esmolol	No	May cause beta blockage in fetus	Probably compatible No published information
Carvedilol	Limited Information	May increase risk of growth restriction	Probably compatible No published information
Calcium Channel Blockers			
Verapamil	No	No adverse fetal effects	Probably compatible
Nifedipine	No	No adverse fetal effects	Probably compatible
Diltiazem	No	No adverse fetal effects	Probably compatible Limited information
Amlodipine	No	No adverse fetal effects Limited human information, animal data suggest risk	Probably compatible Limited information
Antiarrhythmic Agents			
Lidocaine	No	No adverse fetal effects	Probably compatible
Procainamide	No Limited human information	Limited human information	Probably compatible Limited information
Phenytoin	Yes	Potential for early hemorrhagic disease of the newborn	Probably compatible

Drug	Teratogenic	Fetal Effects	Breastfeeding
Amiodarone	No	May be associated with fetal thyroid toxicity	Hazardous
Flecainide	Yes	Limited human information	Probably compatible
	Limited human information		Limited information
Sotalol	No	Human data suggest fetal risk	Possibly hazardous
	Limited human information		
AV Node Blocking Agents			
Adenosine	No Information	No adverse fetal effects	Probably compatible
			No published information
Digoxin	No	No adverse fetal effects	Probably Compatible
Anticoagulants and Anti-Thrombotics			
Warfarin	Yes	Risk of fetal hemorrhage	Probably compatible
Low-molecular-weight heparin	No	No adverse fetal effects	Probably compatible
		Does not cross placenta	
Unfractionated heparin	No	No adverse fetal effects	Probably compatible
		Does not cross placenta	
Clopidogrel	No	Limited human information	Probably compatible
	Limited human information		No published information
Direct Factor Xa Inhibitors (rivaroxaban or apixaban)			
	No	Product labeling warns about abnormal bleeding risk	Possibly hazardous
		Crosses placenta	No published information
Diuretics			
Hydrochlorothiazide	No	No adverse fetal effects	Probably compatible
Furosemide	No	No adverse fetal effects	Probably compatible
			No published information

* For additional information on an individual medication's risk with breastfeeding, see https://toxnet.nlm.nih.gov/lactmed.htm.

Data from Hale TW. Hale's medications and mothers' milk: a manual of lactational pharmacology. 18th ed. New York (NY): Springer; 2019 and Briggs GG, Freeman RK, Towers CV, Forinash AB. Drugs in pregnancy and lactation. 11th ed. Philadelphia (PA): Wolters Kluwer; 2017.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARRIE M CERESA
10/16/2020 06:09:29 PM

MIRIAM C DINATALE
10/16/2020 06:28:06 PM

LYNNE P YAO
10/19/2020 06:26:25 AM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 214377
Submission Number	001
Submission Date	5/21/2020
Date Consult Received	6/18/2020
Drug Name	Vericiguat
Indication	Treatment of chronic heart failure (HFrEF)
Therapeutic dose	10 mg once daily with food
Clinical Division	Division of Cardiology and Nephrology (DCN)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 6/18/2020 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT reviews under IND 116743 dated 05/09/2016, 11/03/2017 and 01/24/2018 in DARRTS (link)
- Study Report 18979 (Submission 0001)
- Study Report P001MK1242 (VICTORIA) (Submission 0001)
- Proposed Labeling (Submission 0001)
- Highlights of Clinical Pharmacology and Cardiac Safety (Submission 0001)

1 SUMMARY

1.1 TQT STUDY FINDINGS

No large mean increases in the QTc interval were detected in the TQT study. Small increases in QTc interval could not be excluded due to limitations in the study design.

The effect of vericiguat was evaluated in a multicenter, randomized, 2-arm, placebo and active-controlled study including a vericiguat multiple-dose part with fixed up-titration periods and with moxifloxacin as the positive control in 72 patients (BAY 1021189, study id: 18979). The highest dose of vericiguat evaluated was 10 mg once daily with food in patients which is the targeted maintenance dose and the maximum tolerated dose. The study design had multiple limitations: (1) there was single baseline in the beginning of the study, (2) there was no washout time between periods, and (3) there was no concurrent placebo administration. Thus, ΔΔQTcF could not be derived. Furthermore, ECG data were only collected for 7-hour postdose for moxifloxacin which did not allow for evaluation of the timecourse of the QTc response.

The data from BAY 1021189 were analyzed using by-timepoint analysis as the primary analysis. However, due to these limitations in the study design, the data were presented using descriptive statistics for time-matched change from baseline of QTcF, which did not

suggest that vericiguat is associated with significant QTc prolonging effect in the QTc interval (refer to section 4.3) – see Table 1 for result. The moxifloxacin response appeared to show assay sensitivity as the largest lower bound of 90% CI of mean increase in QTc values was greater than 5 msec (Table 1). However, the typical 24-hour time time-course in response was not available.

Table 1: The Point Estimates and the 90% CIs

Treatment	Day	Time (Hours)	ΔQTcF (msec)	90.0% CI (msec)
Vericiguat 2.5 mg	14	4.5	1.0	(-1.2 to 3.1)
Vericiguat 5 mg	14	4.5	2.4	(0.4 to 4.4)
Vericiguat 10 mg	14	4.5	3.7	(1.6 to 5.9)
Moxifloxacin 400 mg	8	4.0	12.9	(10.8 to 15.1)

For further details on the FDA analysis, please see section 4.

1.2 INTEGRATED NONCLINICAL AND CLINICAL ASSESSMENT

The sponsor evaluated the potential for vericiguat to block the hERG potassium channel and prolong the QTc interval in an in vivo QT study in dogs. Because the nonclinical evaluation did not follow best practices (see section 3.1.2 for details), the results of these studies cannot be included in an integrated risk assessment as described in the new ICH S7B Q&As.

1.3 COMMENTS TO THE REVIEW DIVISION

Requests from the Division: We request a consult to evaluate both TQT study data and the ECG data in the phase 3 study-VICTORIA for vericiguat (NDA 214377). We have noted an trend toward increased mortality and HF hospitalizations in subjects without ICD/CRT/CRT-D devices, and thus have interest in the toxicology data showing some but relatively mild inhibitory effects on hERG and the sodium channel current. Therefore, we are interested in the evaluation of changes in the QRS duration (as well as the PR and RR) in both TQT study and the ECG data in VICTORIA including the analyses of central tendency, outliers and cumulative distribution functions. The role of baseline device use should be considered when conducting the analyses (i.e. paced rhythms excluded).

IRT's response:

As the division requested, we evaluated both BAY 1021189 study and VICTORIA study data sets. In BAY 1021189 study, data appeared to show no significant mean increase or decrease in PR and QRS. Outlier analysis of BAY 1021189 study shows that none of the subjects was in the outlier category for PR and QRS.

Categorical analysis results for VICTORIA study do not show imbalances in the percent increases in the PR and QRS intervals for vericiguat in patients with no device compared to patients with biventricular pacemaker only, ICD only or ICD and biventricular pacemaker groups.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to Submission 001 (link) from the IRT. Our changes are highlighted (addition, ~~deletion~~). Our changes are for suggestions only and we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Merck is developing vericiguat (BAY 1021189), a soluble guanylate cyclase (sGC) stimulator, for the indication to reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a worsening HF event, in adults with symptomatic chronic HF, in combination with other HF therapies. The recommended starting dose of vericiguat is 2.5 mg once daily. Vericiguat dose is doubled approximately every 2 weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient. Vericiguat dose is administered with food.

Previously the IRT reviewed the sponsor's dedicated QT study protocol 18979 under IND 116743. Study 18979 was planned as a randomized, 2-arm, placebo- and positive-controlled study including a fixed up-titration period of vericiguat in 72 patients. The vericiguat treatments were 2.5 mg QD x14 days followed by 5 mg QD x14 days and 10 mg QD x14 days, administered with food. A 14-day placebo treatment period (including a single dose of moxifloxacin 400 mg on Day 8 of the placebo period) was planned before or after the vericiguat treatments. The primary analysis was by-timepoint analysis of QTcF at 10 mg QD x14 days. The sponsor was advised to design the study using a parallel nested crossover study design (IRT review dated 11/03/2017 in DARRTS). In a meeting with the Agency on 11/29/2017, the Agency acknowledged the sponsor's feasibility issues and proposed to evaluate the QT prolongation risk based on the totality of the data

encompassing preclinical assessment and ECG assessments planned in Phase 3 studies (IRT review under dated 01/24/2018 in DARRTS).

In the current submission, the proposed therapeutic dose and primary analysis method for Study 18979 remained the same. According to the sponsor, ECGs were recorded on validated digital automated ECG machines and they were placed in a central ECG repository. The sponsor used ECG data derived from the computer-assisted method. Data from Day 14 of the placebo period (treatment D) was used for placebo correction. The reviewers conducted by-timepoint analysis, concentration-QTc analysis and categorical analysis for study 18979. Because the study does not have concurrent placebo for vericiguat or moxifloxacin treatments, ΔΔQTcF cannot be properly derived.

The sponsor also provided ECG data from Phase 3 study VICTORIA. This is a randomized, parallel-group, placebo-controlled, double-blind, event-driven, Phase 3 study in subjects with Heart Failure With Reduced Ejection Fraction (HFrEF). 2519 patients were treated with at least 1 dose of vericiguat and 2515 patients were treated with at least 1 dose placebo. This trial includes a dose titration regimen based on a subject's sitting SBP. 12-lead ECG were collected at randomization (Day 1), Week 16, and at the time of Efficacy Cut-off. The reviewers conducted categorical analysis for VICTORIA study.

Highlight of clinical pharmacology: According to the sponsor's proposed label, the pharmacokinetics of the vericiguat are characterized by an absorption phase that has a Tmax of 4 (b) (4) hours in the fed state. Accumulation of vericiguat at steady state after 10 mg once daily dosing is about 1.7 fold for AUC and 1.5 fold for Cmax. The terminal elimination half-life in patients is 30 hours. Population PK model predicted steady state AUC is 6680 µg*hr/L and Cmax is 350 µg/L at the 10 mg QD dose. Glucuronidation is the major biotransformation pathway leading to an N-glucuronide metabolite which is pharmacologically inactive. A radiolabeled dose of vericiguat showed that 53 % of the dose was recovered in urine mostly as N-glucuronide and 45 % of the dose was recovered in feces primarily as vericiguat. High fat meal increases vericiguat Cmax by 41%. Other intrinsic/extrinsic factors do not significantly increase vericiguat Cmax; maximum effect was 21% increase in unbound Cmax and 16% increase in total Cmax, in patients with severe renal impairment. The effect of severe hepatic impairment is not known.

3.1.2 Nonclinical Safety Pharmacology Assessments

In safety pharmacology studies addressing the risk for QT interval prolongation in humans, no clinically relevant findings were observed in cardiovascular in vitro and in vivo studies (i.e., hERG potassium ion channel assay and QT/ QTc intervals in the ECG recordings of Beagle dogs):

- The concentrations required to inhibit hERG potassium current by 20% (IC20: 1.9 µM) and by 50% (IC50: 9.9 µM) were approximately 106-fold and 553-fold, respectively, the human plasma Cmax,u,ss at the maximum recommended human dose (MRHD; 10 mg/day).
- There were no signs of QT/QTc prolongation observed in studies with vericiguat in telemetered Beagle dogs up to 26-fold the human plasma Cmax,u,ss at the MRHD.

In safety pharmacology studies in conscious, telemetered dogs, on-target mediated hemodynamic effects (reduction of arterial blood pressure with concomitant increased heart rate) were observed at plasma concentrations approximately 4-fold the human plasma Cmax,u,ss at the (MRHD).

Reviewer's assessment: *The sponsor evaluated the effects of vericiguat on hERG current, a surrogate for IKr that mediate membrane potential repolarization in cardiac myocytes. The hERG study report (link) describes the potential effects of vericiguat on the hERG current in HEK293 cells. The hERG current was assessed at room temperature, using a voltage protocol consisting of a depolarizing step from -80 mV to +20 mV (1000 ms), followed by a repolarizing step to -120 mV (500 ms). The voltage waveform was repeated every 12 seconds. The sponsor's voltage protocol to evoke the hERG current is significantly different from the recommended hERG current protocol by the FDA (link).High concentration of E-4031 (1 µM) was used as the positive control. Leak subtractions were not performed in this study. In addition, samples of the test article formulation solutions from the outflow of the perfusion apparatus were not analyzed for concentration verification The consequences of these protocol deviations on drug pharmacology are unclear.*

Vericiguat (acute exposure) caused a concentration-dependent inhibition of hERG current with an IC50 value of 9.9 µM. The hERG safety margin of vericiguat is summarized below:

Table 2: Safety Margin of vericiguat on hERG Current

	Cmax (ng/mL)	Protein Binding	Free Cmax (ng/mL)	hERG IC50 (µM)	Mol Weight (g/mol)	Safety Margin (Ratio)
vericiguat	350	97.8 %	7.7	9.9	426.36	548x

Study A50538(link) (GLP compliant) evaluated effects of a single dose of oral administration of vericiguat (BAY 1021189) on 4 conscious telemetered Beagle dogs at 0.6, 2, and 6 mg/kg as well as reference/vehicle treatment. The corresponding vericiguat plasma C_{max} values were 270, 848 and 1949 ng/mL, respectively. The doses tested in this study adequately covered therapeutic exposure level in humans (350 ng/mL; sponsor's ClinPharm Table). Vericiguat caused dose-dependent decreases in both diastolic (-17% at 6 mg/kg) and systolic (-23% at 6 mg/kg) arterial blood pressures, a dose-dependent increase in hear rate (+68% at 6 mg/kg). However, vericiguat had no significant effects on QRS and QTc intervals. The sponsor didn't provide the PR interval data in the study.

In summary, results from experiments that conducted by sponsor suggest that vericiguat does not acutely interact with hERG channels at the therapeutic exposure level. While the results of the hERG assay do not indicate a potential for acute inhibition of hERG (a safety margin of 548x), it should be noted that the assay deviated from the best practice recommended and therefore can not be included in an integrated risk assessment.

Vericiguat caused dose-dependent decreases in both diastolic and systolic blood pressures in conscious Beagle dogs, consistent with its vasodilating effect by directly increasing cyclic guanosine monophosphate (cGMP) synthesis in smooth muscle. However, the in vivo study may fail to pick up small QT interval changes since there was no positive control in the study, and the increased heart rate (> 50 bpm) by vericiguat may also make it a challenge to assess small QT interval changes.

3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

Sponsor's analysis shows that Vericiguat excluded the 20 msec threshold at the therapeutic dose level for ΔQTcF.

Sponsor's analysis plan was as follows: The individual change from baseline of QTcF after 14 days of dosing with 10 mg vericiguat or placebo will be analyzed by an analysis of covariance (ANCOVA) separately for each time point, including the factors sequence, period and treatment (10 mg vericiguat [Day 14 of Treatment C and C*] and placebo [Day 14 of Treatment D]) as fixed effects, the factor subject(sequence) as random effect and the baseline value as covariate. Based on these analyses, point estimates (LS-Means) and confirmatory two-sided 90% confidence intervals of the true mean difference " 10 mg vericiguat at steady state [Day 14 of Treatment C and C*] – placebo [Day 14 of treatment D]" will be calculated for each time point on Day 14 of Treatment C and C* for 10 mg vericiguat. The comparison of 10 mg vericiguat at steady state vs. placebo will be performed as a noninferiority test.

Reviewer's comment: *Design of this study had multiple limitations. There was single baseline in the beginning of the study and there was no washout time between periods and no concurrent placebo administration. Due to these limitations of the study design, FDA reviewer presented descriptive statistics for ΔQTcF, ΔHR, ΔPR and ΔQRS. Please see section 4.3 for additional details.*

3.2.1.1 Assay Sensitivity

Sponsor claims assay sensitivity was established by the moxifloxacin arm.

Reviewer's comment: *FDA reviewer's analysis also shows that the assay sensitivity was established, sponsor collected PD data till hour 7 and PK data till hour 5. So study is lacking typical 24-hour moxi profile.*

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline, PR (>220 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline) in BAY 1021189 study. One subject experienced HR greater than 100 beats/min in BAY 1021189 study.

In VICTORIA study, there were 283 subjects who experienced QTcF greater than 500 msec and 126 subjects with ΔQTcF greater than 60 msec.

Reviewer's comment: *FDA reviewer's results are similar to the sponsor's results for BAY 1021189 study. In VICTORIA study, FDA reviewer's results are similar to the sponsor's results for* ΔQTcF. *FDA reviewer could not locate categorical analysis for HR, PR and QRS for VICTORIA study. For categorical analysis of both BAY 1021189 study and VICTORIA study, please see section 4.4.*

3.2.3 Exposure-Response Analysis

The sponsor conducted linear regression analysis of the placebo-corrected change from baseline QTcF after treatment with 2.5 mg, 5 mg and 10 mg vericiguat at steady state versus the plasma concentrations of vericiguat. The model included concentration as a fixed continuous effect and subject as random effect. The sponsor reported a slight relationship of vericiguat plasma concentration to QTcF prolongation at steady state (day 14) (intercept: 0.7975; slope=0.007640).

Reviewer's comment: *The reviewer conducted concentration-QTc analysis using ΔQTcF as the dependent variable. Please refer to section 4.5 for reviewer's analysis.*

3.2.4 Safety Analysis

There were no deaths or TEAEs with severe intensity reported in this study. There were two SAEs reported, an acute cholecystitis of moderate intensity in subject (b) (6) which was considered as medically important serious event, and infected atheroma on the back of subject (b) (6), that was of moderate intensity and required hospitalization. In both cases, the subjects continued study treatment and the events were considered related to neither vericiguat nor moxifloxacin.

Three treatment-emergent adverse events led to discontinuation of the study treatment in two subjects: Subject (b) (6) treated in sequence A*-B-C-D, left the study after completion of the first treatment period due to pitting edema of moderate intensity and pain in the leg of mild intensity, while subject (b) (6), treated in sequence D-A-B-C*, stopped placebo intake in Treatment D after Day 4, prior to moxifloxacin intake, due to diarrhea of moderate intensity. In subject (b) (6) pitting edema was not considered related to any study drug, and the event "pain in the leg" was considered related to moxifloxacin, but not to vericiguat, while the subject only received vericiguat 2.5 mg as active drug. In subject (b) (6), the TEAE was considered related to vericiguat and not to moxifloxacin, while the subject only received placebo.

There was 1 cardiac-related TEAE reported with vericiguat 5 mg: subject (b) (6) experienced atrial flutter of moderate intensity lasting 5 days. In addition, 2 subjects reported TEAEs of QT interval prolonged of mild intensity; however, none of the subjects experienced QTcF greater than 480 msec or ΔQTcF greater than 60 msec.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF (Fridericia) for the primary analysis which is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

Not Applicable.

4.3 BY TIME ANALYSIS

The analysis population used for by time analysis included all subjects with a baseline and at least one post-dose ECG. Statistical reviewer performed by-time analysis for BAY 1021189 study only. Study design had multiple shortcomings. There were no concurrent placebos for all treatments and only one baseline in the beginning of the study. There was no washout time in between periods. Thus, ΔΔQTcF can not be properly derived. Considering these limitations, the statistical reviewer evaluated the ΔQTcF effect using parametric descriptive statistics for QTcF, HR, PR and QRS.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for different treatment groups. The maximum ΔQTcF values by treatment are shown in Table 3. Statistical reviewer also looked at ΔQTcF values by sequence are shown is Figure 2 and compared those sequences. There were no statistically significant differences between two sequences except few time points in vericiguat 5mg dose level. Based on this findings, FDA statistical reviewer pooled two sequences together.

Figure 1: Mean and 90% CI of ΔQTcF Time Course (unadjusted CIs).

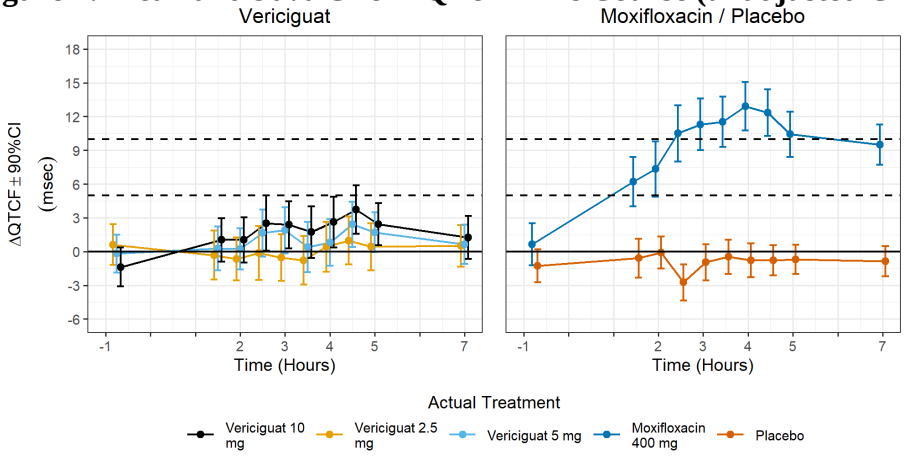
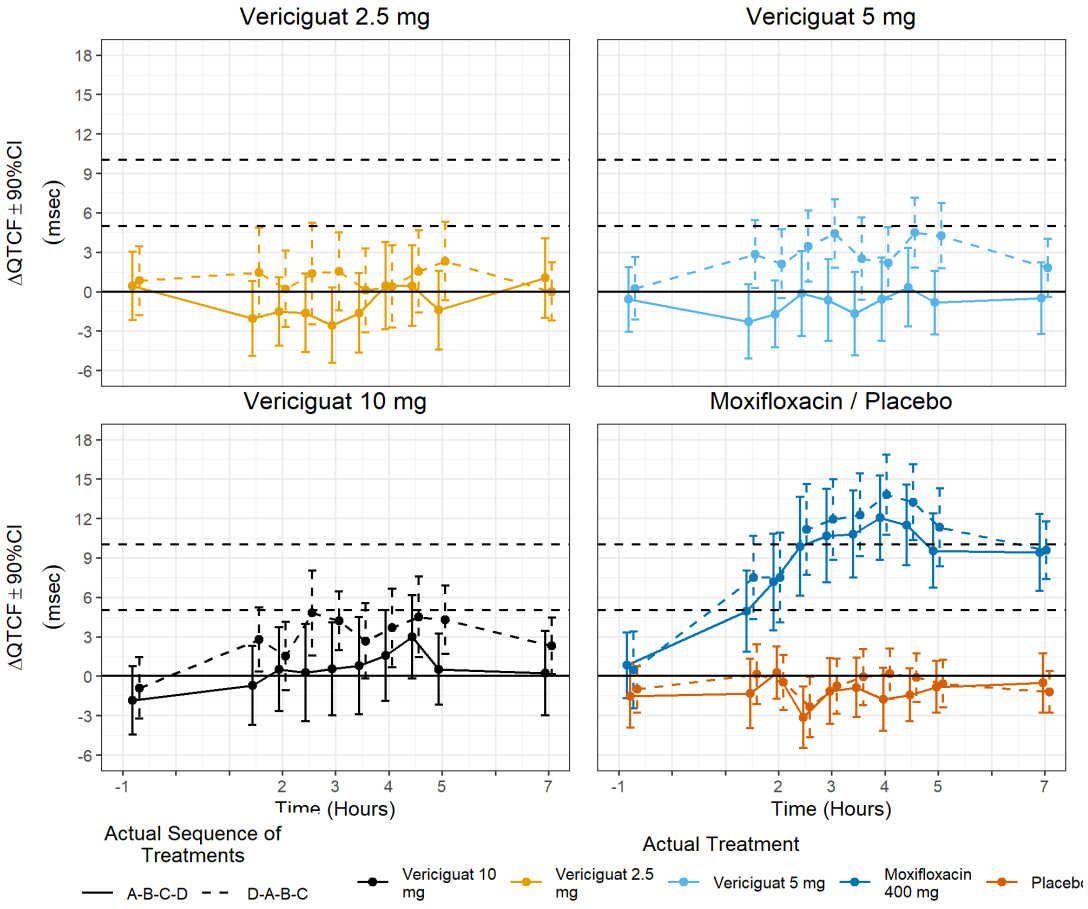


Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔQTcF

Treatment	Analysis Nominal Period Day (C)	N	Time (Hours)	ΔQTcF (msec)	90.0% CI (msec)
Vericiguat 2.5 mg	14	73	4.5	1.0	(-1.2 to 3.1)
Vericiguat 5 mg	14	72	4.5	2.4	(0.4 to 4.4)
Vericiguat 10 mg	14	72	4.5	3.7	(1.6 to 5.9)

Treatment	Analysis Nominal Period Day (C)	N	Time (Hours)	ΔQTcF (msec)	90.0% CI (msec)
Moxifloxacin 400 mg	8	72	4.0	12.9	(10.8 to 15.1)
Placebo	14	72	2.0	-0.1	(-1.5 to 1.3)

Figure 2: Mean and 90% CI of ΔQTcF Time Course for two sequences separately (unadjusted CIs).



4.3.1.1 Assay sensitivity

The statistical reviewer evaluated the ΔQTcF effect for moxifloxacin using parametric descriptive statistics. The time-course of changes in ΔQTcF is shown in Figure 1 and shows the expected time-profile with a mean effect of > 5 msec after Bonferroni adjustment for 4 time points (Table 4).

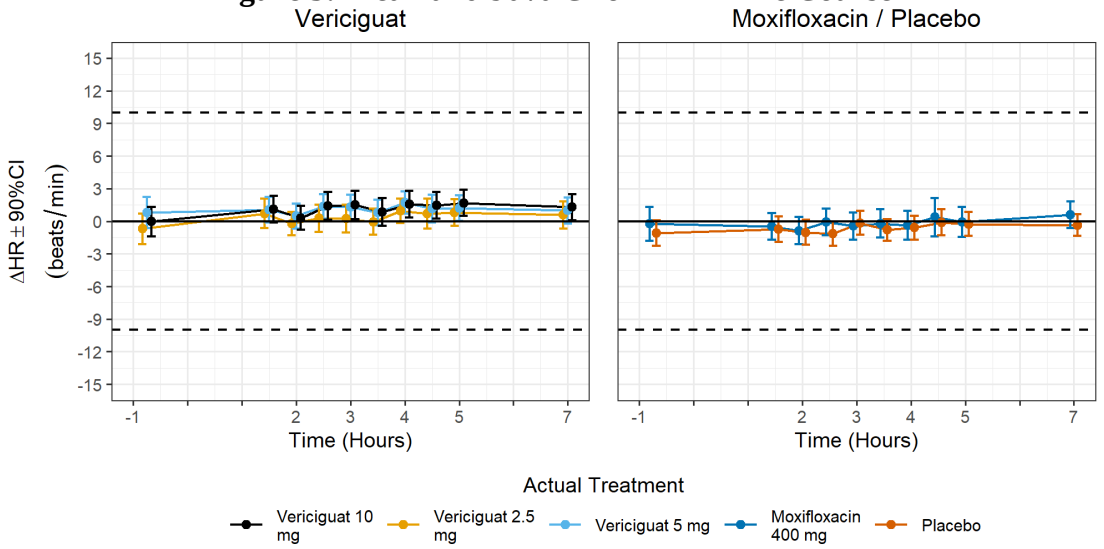
Table 4: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔQTcF

Treatment	Analysis Nominal Period Day (C)	N	Time (Hours)	ΔQTCF (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	8	72	4.0	12.9	(10.8 to 15.1)	(9.9 to 15.9)
Placebo	14	72	2.0	-0.1	(-1.5 to 1.3)	(-2.1 to 1.8)

4.3.2 HR

Figure 3 displays the time profile of ΔHR for different treatment groups.

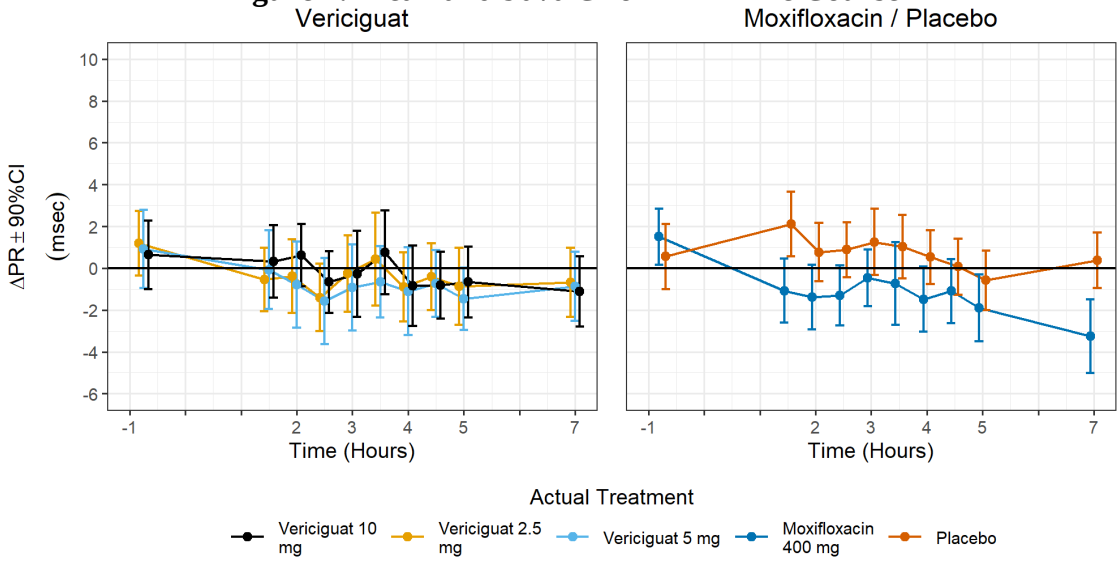
Figure 3: Mean and 90% CI of ΔHR Time Course



4.3.3 PR

Figure 4 displays the time profile of ΔPR for different treatment groups.

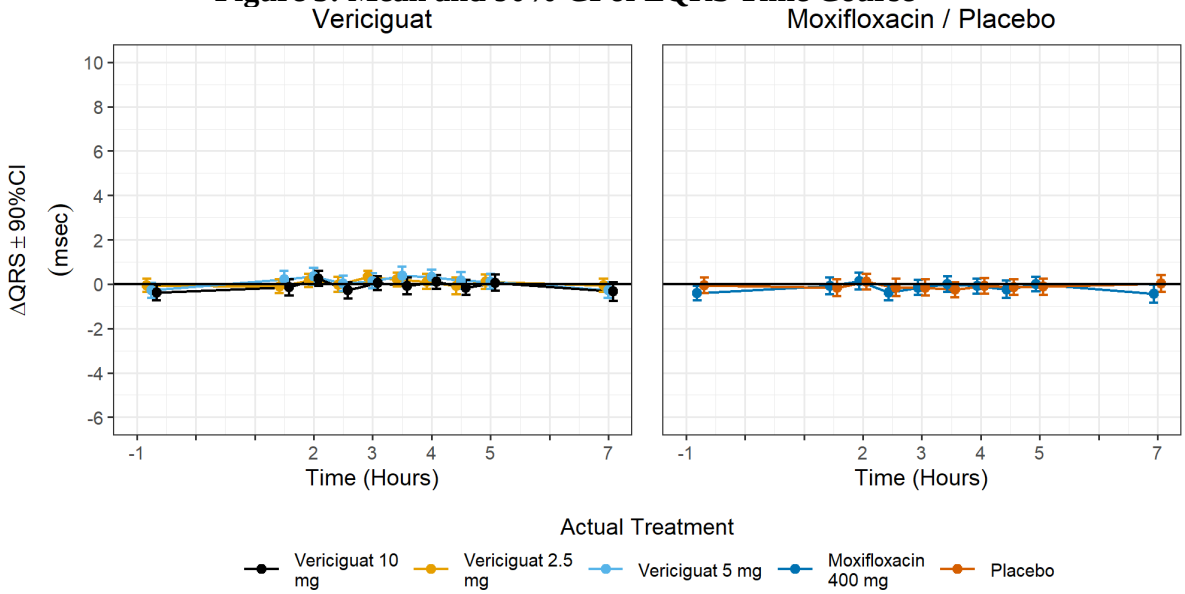
Figure 4: Mean and 90% CI of ΔPR Time Course



4.3.4 QRS

Figure 5 displays the time profile of ΔQRS for different treatment groups.

Figure 5: Mean and 90% CI of ΔQRS Time Course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs. FDA reviewer performed categorical analysis for two studies (BAY 1021189 and VICTORIA) and presented the results separately for QTcF, HR, PR and QRS. If a category is omitted that means that no subjects had values in that category.

4.4.1 QTcF

None of the subjects experienced QTcF greater than 480 msec or ΔQTcF greater than 60 msec in study BAY 1021189 for different levels of vericiguat.

Table 5 lists the number of subjects as well as the number of observations whose QTc values were ≤ 450 msec, between 450 and 480 msec, between 480 and 500 msec and greater than 500 msec with or without a change from baseline greater than 60 msec in VICTORIA study. There were 126 subjects in vericiguat group who experienced QTcF greater than 500 msec and ΔQTcF greater than 60 msec out of 2247 subjects.

Table 5: Categorical Analysis for QTc (maximum) in VICTORIA study

Treatment	DEVICE	Total (N)		Value <= 450 msec		450 msec < Value <= 480 msec		480 msec < Value <= 500 msec		Value > 500 msec & < 60 msec		Value > 500 msec & >= 60 msec	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Vericiguat	Biventricular Pacemaker Only	104	196	19 (18.3%)	45 (23.0%)	17 (16.3%)	39 (19.9%)	25 (24.0%)	48 (24.5%)	38 (36.5%)	58 (29.6%)	5 (4.8%)	6 (3.1%)
Vericiguat	ICD Only	398	822	140 (35.2%)	381 (46.4%)	104 (26.1%)	200 (24.3%)	49 (12.3%)	99 (12.0%)	63 (15.8%)	96 (11.7%)	42 (10.6%)	46 (5.6%)
Vericiguat	ICD and Biventricular Pacemaker	228	443	35 (15.4%)	105 (23.7%)	46 (20.2%)	93 (21.0%)	37 (16.2%)	84 (19.0%)	93 (40.8%)	139 (31.4%)	17 (7.5%)	22 (5.0%)

Treatment	DEVICE	Total (N)		Value <= 450 msec		450 msec < Value <= 480 msec		480 msec < Value <= 500 msec		Value > 500 msec & < 60 msec		Value > 500 msec & >= 60 msec	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Vericiguat	No Device	1517	2925	736 (48.5%)	1772 (60.6%)	428 (28.2%)	664 (22.7%)	165 (10.9%)	243 (8.3%)	126 (8.3%)	175 (6.0%)	62 (4.1%)	71 (2.4%)
Placebo	Biventricular Pacemaker Only	88	173	11 (12.5%)	35 (20.2%)	19 (21.6%)	40 (23.1%)	17 (19.3%)	35 (20.2%)	35 (39.8%)	55 (31.8%)	6 (6.8%)	8 (4.6%)
Placebo	ICD Only	389	761	124 (31.9%)	321 (42.2%)	103 (26.5%)	200 (26.3%)	66 (17.0%)	113 (14.8%)	61 (15.7%)	88 (11.6%)	35 (9.0%)	39 (5.1%)
Placebo	ICD and Biventricular Pacemaker	230	427	34 (14.8%)	96 (22.5%)	40 (17.4%)	93 (21.8%)	43 (18.7%)	78 (18.3%)	94 (40.9%)	137 (32.1%)	19 (8.3%)	23 (5.4%)
Placebo	No Device	1538	2962	715 (46.5%)	1736 (58.6%)	459 (29.8%)	732 (24.7%)	166 (10.8%)	238 (8.0%)	151 (9.8%)	206 (7.0%)	47 (3.1%)	50 (1.7%)

Table 6 lists the categorical analysis results for ΔQTcF (less than 30 msec, between 30 and 60 and greater than 60 msec) in VICTORIA study. There were 222 subjects who experienced ΔQTcF greater than 60 msec in vericiguat group.

Table 6: Categorical Analysis for ΔQTcF (maximum) in VICTORIA study

Treatment	DEVICE	Total (N)		Value <= 30 msec		30 msec < Value <= 60 msec		Value > 60 msec	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Vericiguat	Biventricular Pacemaker Only	104	196	78 (75.0%)	160 (81.6%)	19 (18.3%)	26 (13.3%)	7 (6.7%)	10 (5.1%)
Vericiguat	ICD Only	398	822	284 (71.4%)	665 (80.9%)	58 (14.6%)	91 (11.1%)	56 (14.1%)	66 (8.0%)
Vericiguat	ICD and Biventricular Pacemaker	228	443	172 (75.4%)	364 (82.2%)	32 (14.0%)	46 (10.4%)	24 (10.5%)	33 (7.4%)
Vericiguat	No Device	1517	2925	1172 (77.3%)	2461 (84.1%)	210 (13.8%)	279 (9.5%)	135 (8.9%)	185 (6.3%)
Placebo	Biventricular Pacemaker Only	88	173	70 (79.5%)	143 (82.7%)	10 (11.4%)	17 (9.8%)	8 (9.1%)	13 (7.5%)
Placebo	ICD Only	389	761	264 (67.9%)	598 (78.6%)	68 (17.5%)	94 (12.4%)	57 (14.7%)	69 (9.1%)
Placebo	ICD and Biventricular Pacemaker	230	427	162 (70.4%)	341 (79.9%)	46 (20.0%)	56 (13.1%)	22 (9.6%)	30 (7.0%)
Placebo	No Device	1538	2962	1171 (76.1%)	2492 (84.1%)	247 (16.1%)	326 (11.0%)	120 (7.8%)	144 (4.9%)

4.4.2 HR

Table 7 and Table 8 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min) for study BAY 1021189 and VICTORIA study. One subject in BAY 1021189 experienced HR greater than 100 beats/min in vericiguat 5 mg group. One hundred seventy subjects in VICTORIA study experienced HR greater than 100 beats/min in vericiguat group.

Table 7: Categorical Analysis for HR (maximum)

Treatment	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Vericiguat 2.5 mg	73	1839	73 (100.0%)	1839 (100.0%)	0 (0%)	0 (0%)
Vericiguat 5 mg	72	1440	71 (98.6%)	1439 (99.9%)	1 (1.4%)	1 (0.1%)
Vericiguat 10 mg	72	1799	72 (100.0%)	1799 (100.0%)	0 (0%)	0 (0%)
Placebo	73	1447	73 (100.0%)	1447 (100.0%)	0 (0%)	0 (0%)

VICTORIA Study:

Table 8: Categorical analysis for HR (maximum)

Treatment	DEVICE	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Vericiguat	Biventricular Pacemaker Only	105	198	100 (95.2%)	193 (97.5%)	5 (4.8%)	5 (2.5%)
	ICD Only	398	828	376 (94.5%)	804 (97.1%)	22 (5.5%)	24 (2.9%)
	ICD and Biventricular Pacemaker	228	446	222 (97.4%)	439 (98.4%)	6 (2.6%)	7 (1.6%)
	No Device	1525	2949	1386 (90.9%)	2787 (94.5%)	139 (9.1%)	162 (5.5%)
Placebo	Biventricular Pacemaker Only	89	175	87 (97.8%)	172 (98.3%)	2 (2.2%)	3 (1.7%)
	ICD Only	390	768	364 (93.3%)	739 (96.2%)	26 (6.7%)	29 (3.8%)
	ICD and Biventricular Pacemaker	234	437	227 (97.0%)	430 (98.4%)	7 (3.0%)	7 (1.6%)
	No Device	1549	2990	1408 (90.9%)	2823 (94.4%)	141 (9.1%)	167 (5.6%)

4.4.3 PR

None of the subjects experienced PR greater than 220 msec and 25% increase from baseline in BAY 1021189 study. Table 9 lists the categorical analysis results for PR (less than 200 msec; between 200 and 220 msec and above 220 msec with and without 25% increase over baseline) in VICTORIA study. Fifty two subjects experienced PR greater than 220 msec and 25% increase from baseline in VICTORIA study.

Table 9: Categorical Analysis for PR for VICTORIA study

Treatment	DEVICE	Total (N)		Value <= 220 msec		Value > 220 msec & < 25%		Value > 220 msec & >= 25%	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Vericiguat	Biventricular Pacemaker Only	28	45	22 (78.6%)	37 (82.2%)	3 (10.7%)	4 (8.9%)	3 (10.7%)	4 (8.9%)

Treatment	DEVICE	Total (N)		Value <= 220 msec		Value > 220 msec & < 25%		Value > 220 msec & >= 25%	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Vericiguat	ICD Only	240	458	174 (72.5%)	360 (78.6%)	50 (20.8%)	78 (17.0%)	16 (6.7%)	20 (4.4%)
Vericiguat	ICD and Biventricular Pacemaker	52	85	45 (86.5%)	75 (88.2%)	5 (9.6%)	7 (8.2%)	2 (3.8%)	3 (3.5%)
Vericiguat	No Device	1024	1924	845 (82.5%)	1661 (86.3%)	148 (14.5%)	227 (11.8%)	31 (3.0%)	36 (1.9%)
Placebo	Biventricular Pacemaker Only	16	25	14 (87.5%)	21 (84.0%)	2 (12.5%)	4 (16.0%)	0 (0%)	0 (0%)
Placebo	ICD Only	214	386	157 (73.4%)	316 (81.9%)	40 (18.7%)	51 (13.2%)	17 (7.9%)	19 (4.9%)
Placebo	ICD and Biventricular Pacemaker	58	92	52 (89.7%)	86 (93.5%)	4 (6.9%)	4 (4.3%)	2 (3.4%)	2 (2.2%)
Placebo	No Device	985	1833	816 (82.8%)	1606 (87.6%)	124 (12.6%)	176 (9.6%)	45 (4.6%)	51 (2.8%)

4.4.4 QRS

None of the subjects experienced QRS greater than 120 msec and 25% increase from baseline in BAY 1021189 study. Table 10 lists the categorical analysis results for QRS (less than 120 msec and above 120 msec with and without 25% increase over baseline) in VICTORIA study. One hundred seventy eight subjects experienced QRS greater than 120 msec and 25% increase from baseline in VICTORIA study.

Table 10: Categorical Analysis for QRS in VICTORIA study

Treatment	DEVICE	Total (N)		Value <= 120 msec		Value > 120 msec & < 25%		Value > 120 msec & >= 25%	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Vericiguat	Biventricular Pacemaker Only	104	198	12 (11.5%)	33 (16.7%)	80 (76.9%)	150 (75.8%)	12 (11.5%)	15 (7.6%)
Vericiguat	ICD Only	398	830	155 (38.9%)	405 (48.8%)	189 (47.5%)	354 (42.7%)	54 (13.6%)	71 (8.6%)
Vericiguat	ICD and Biventricular Pacemaker	228	445	32 (14.0%)	90 (20.2%)	165 (72.4%)	320 (71.9%)	31 (13.6%)	35 (7.9%)
Vericiguat	No Device	1524	2939	926 (60.8%)	1940 (66.0%)	517 (33.9%)	895 (30.5%)	81 (5.3%)	104 (3.5%)
Placebo	Biventricular Pacemaker Only	88	173	8 (9.1%)	23 (13.3%)	69 (78.4%)	133 (76.9%)	11 (12.5%)	17 (9.8%)
Placebo	ICD Only	393	774	155 (39.4%)	374 (48.3%)	187 (47.6%)	344 (44.4%)	51 (13.0%)	56 (7.2%)
Placebo	ICD and Biventricular Pacemaker	230	428	22 (9.6%)	59 (13.8%)	168 (73.0%)	315 (73.6%)	40 (17.4%)	54 (12.6%)
Placebo	No Device	1548	2976	912 (58.9%)	1927 (64.8%)	545 (35.2%)	938 (31.5%)	91 (5.9%)	111 (3.7%)

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted using all subjects with baseline and at least one post-baseline ECG with time-matched PK.

4.5.1 QTc

Prior to evaluating the relationship between drug-concentration and QTc using a linear model, the three key assumptions of the model needs to be evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) delay between plasma concentration and ΔQTc and 3) presence of non-linear relationship.

Figure 3 shows the time-course of ΔHR which shows an absence of significant ΔHR changes. Figure 6 shows the time-course of drug-concentration and ΔQTcF. The plot shows dose dependent increase in plasma concentration and it does not suggest significant hysteresis. Figure 7 shows the relationship between drug concentration and ΔQTc and supports the use of a linear model.

Figure 6: Time course of drug concentration (top) and QTc (bottom)

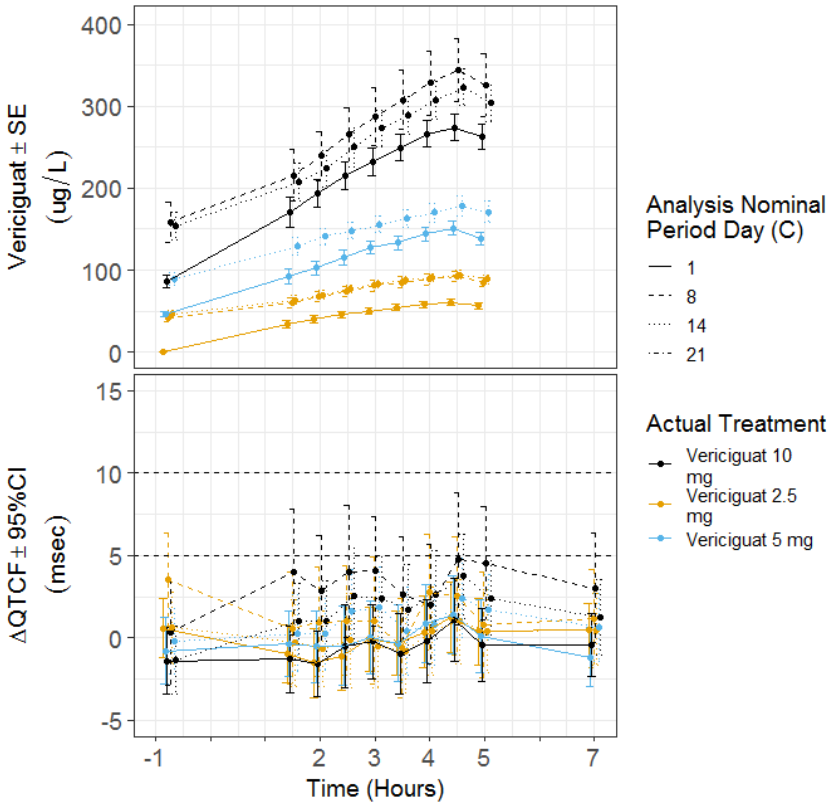
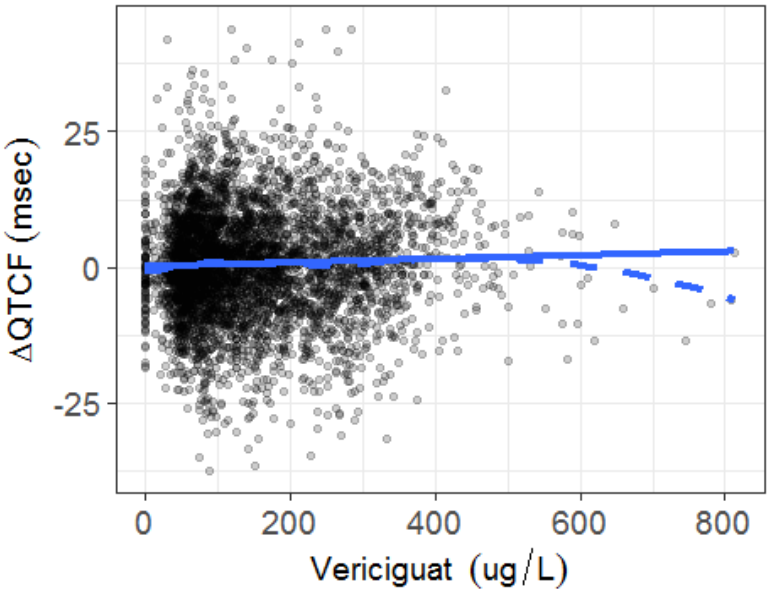


Figure 7: Assessment of linearity of concentration-QTc relationship



Finally, the linear model (ΔQTcF ~ 1+CONC+centered baseline, random effect on the intercept) was applied to the data and the goodness-of-fit plot is shown in Figure 8. The model suggests a statistically significant exposure-response relationship within the studied exposure range (5.78 msec per mg/L; p-value <0.001), however, the predicted ΔQTcF at the 10 mg QD x14 days (0.324 mg/L) does not suggest a large mean increase (i.e. >20 msec) at the therapeutic dose (10 mg QD). Predictions from the concentration-QTc model are provided in Table 11.

Figure 8: Goodness-of-fit plot for QTc

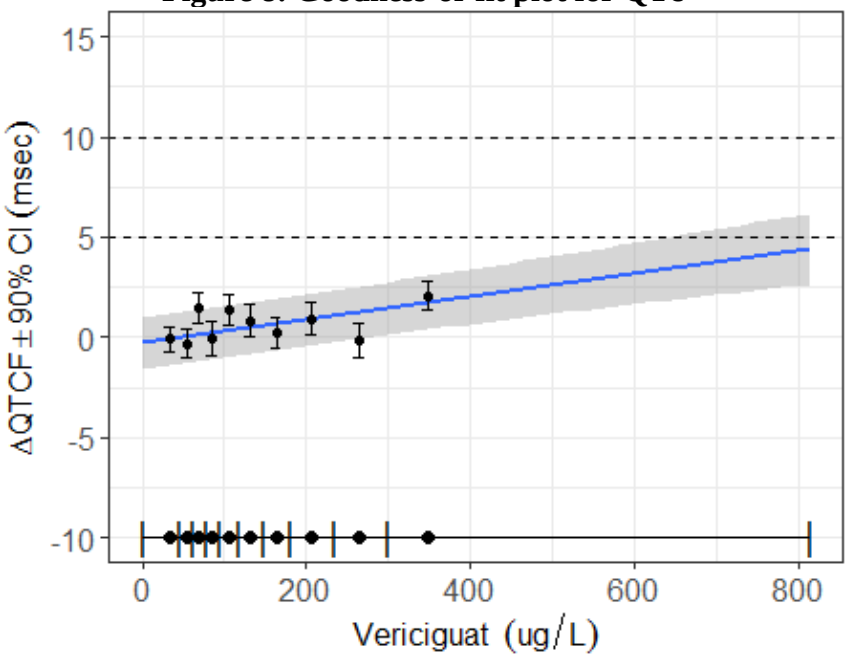


Table 11: Predictions from concentration-QTc model

Actual Treatment	Analysis Nominal Period Day (C)	BAY 1021189 (ug/L)	ΔQTCF (msec)	90.0% CI (msec)
Vericiguat 2.5 mg	8	95.2	0.3	(-1.0 to 1.6)
Vericiguat 2.5 mg	14	96.6	0.3	(-1.0 to 1.6)
Vericiguat 5 mg	14	180.1	0.8	(-0.5 to 2.0)
Vericiguat 10 mg	8	348.5	1.7	(0.4 to 3.1)
Vericiguat 10 mg	14	323.7	1.6	(0.3 to 2.9)

4.5.1.1 Assay sensitivity

Assay sensitivity was established with by-timepoint analysis. Please refer to section 4.3.1.1 for reviewer's analysis.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

FERDOUSE BEGUM
08/25/2020 10:00:56 AM

DALONG HUANG
08/25/2020 10:02:16 AM

RAMAN K BAWEJA
08/25/2020 10:06:32 AM

NAN ZHENG
08/25/2020 10:56:40 AM

DONGLIN GUO
08/25/2020 10:58:19 AM

JOSE VICENTE RUIZ
08/25/2020 11:03:00 AM

MICHAEL Y LI
08/25/2020 11:06:31 AM

LARS JOHANNESEN
08/25/2020 12:41:04 PM

CHRISTINE E GARNETT
08/25/2020 12:46:24 PM