

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**214377Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**



IND 116743

**MEETING MINUTES**

Merck Sharp & Dohme Corp.  
Attention: Tonja Hampton, MD  
Director, Global Regulatory Affairs  
126 E. Lincoln Ave, RY34-B188  
PO Box 2000  
Rahway, NJ 07065

Dear Dr. Hampton:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Vericiguat (MK-1242).

We also refer to the meeting between representatives of your firm and the FDA on February 3, 2020. The purpose of the meeting was to discuss the top line results of your pivotal phase 3 study, VICTORIA (study PN001).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Alexis Childers, Regulatory Project Manager, at (301) 796-0442.

Sincerely,

*{See appended electronic signature page}*

Ellis Unger, M.D.  
Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes and sponsor presentation



## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** C  
**Meeting Category:** Top-Line Results

**Meeting Date and Time:** February 3, 2020, 10:30am-12:00 pm  
**Meeting Location:** White Oak Building 22, Conference Room: 1415

**Application Number:** IND 116743  
**Product Name:** Vericiguat (MK-1242)  
**Indication:** In combination with other heart failure therapies vericiguat is indicated in adult patients (b) (4) chronic heart failure (HF) with ejection fraction below 45 % to reduce the risk of cardiovascular death and heart failure hospitalization.

**Applicant Name:** Merck Sharp & Dohme Corp.

**Meeting Chair:** Ellis Unger M.D.  
**Meeting Recorder:** Alexis Childers

### FDA ATTENDEES

#### *Office of Drug Evaluation I*

Ellis F. Unger, MD Director

#### *Office of Drug Evaluation I, Division of Cardiovascular and Renal Products*

Norman Stockbridge, MD, PhD	Director
Aliza Thompson, MD	Deputy Director
Mary Ross Southworth, PharmD	Deputy Safety Director
Michael Monteleone, MS, RAC	Associate Director of Labeling
Fred Senatore, MD, PhD, FACC	Clinical Team Leader
Preston Dunnmon, MD	Clinical Reviewer
Tzu-Yun McDowell, PharmD	Safety Analyst
Edward Fromm, RPh, RAC	Chief, Project Management Staff
Alexis Childers, RAC, CQIA	Sr. Regulatory Health Project Manager
Tina Sadr, MS	Regulatory Health Project Manager
Brian Cooney, PMS	Regulatory Health Project Manager

#### *Office of Clinical Pharmacology, Division of Clinical Pharmacology I*

Sudharshan Hariharan, PhD Clinical Pharmacology Team Leader

#### *Office of Biometrics, Division of Biometrics I*

Jialu Zhang, PhD Statistical Team Leader

Dali Zhou, PhD

Statistician

## **SPONSOR ATTENDEES**

### ***Merck Team***

Sean Curtis, MD  
Development

Senior Vice President, Global Clinical

Joerg Koglin, MD PhD

Vice President, Global Clinical Development  
Executive Director, Global Clinical Development

Robert Blaustein, MD, PhD

Mahesh Patel, MD

Executive Director, Global Clinical Development

Gregory Golm, PhD

Executive Director, Biostatistics

Gang Jia, PhD

Senior Principal Scientist, Biostatistics

Justo Sierra Johnson, MD

Senior Principal Scientist, Clinical Safety Risk Management

Sandip Roy, PhD

Associate Vice President, Global Regulatory Affairs

Vivian Fuh, MD

Executive Director, Global Regulatory Affairs

Tonja Hampton, MD

Director, Global Regulatory Affairs

Lina AlJuburi, PharmD, MS

Director, Global Regulatory Policy

### ***Bayer Team***

Richard Nkulikiyinka, MD

Vice President, Clinical Development

Lothar Roessig, MD

Global Clinical Leader, Clinical Development

Vanja Vlajnic

Statistician, Clinical Statistics

Regina Seidel

Head, Regulatory Strategy, Cardiology & Nephrology

Robert Kraemer, PhD

Global Program Head

## **1.0 BACKGROUND**

Vericiguat is a soluble guanylate cyclase (sGC) stimulator being co-developed by Merck and Bayer for the treatment of chronic heart failure (NYHA class II-IV) in adults with reduced (HFrEF) left ventricular ejection fraction (LVEF <45%) in addition to standard of care to reduce the risk of cardiovascular death (CV) and heart failure hospitalization.

Vericiguat was granted Fast Track Designation in 2014 for HFrEF. An EOP2 meeting was held in 2015 after completion of a phase 2b study (Study 15371- SOCRATES-REDUCED). At the meeting, the Division agreed that a single trial could be sufficient to submit a marketing application with a p-value substantially <0.05, and the mortality component trending in a positive direction. The global clinical trial, VeriCiguaT gLObal study in patients with heart failure and Reduced ejection frAction (VICTORIA), commenced in 2016 and concluded in 2019.

The purpose of this meeting was to discuss the topline results of the VICTORIA trial.

**U.S. Food and Drug Administration**

Silver Spring, MD 20993

[www.fda.gov](http://www.fda.gov)

## 2. DISCUSSION

Merck presented the attached slides. Highlights from the discussion are summarized below.

Introduction: Merck began the discussion by presenting an overview of the recently completed VICTORIA Phase 3 trial, emphasizing the study design and analyses for safety and efficacy. The study evaluated vericiguat vs placebo on a background of standard care in patients with heart failure with reduced ejection fraction (HFrEF). The primary endpoint was time to first occurrence of cardiovascular (CV) death or heart failure (HF) hospitalization. Secondary endpoints included time to CV death, time to first HF hospitalization, time to total HF hospitalizations (including recurrent events), time to first occurrence of the composite of all-cause mortality or HF hospitalization, and time to all-cause mortality.

Of the 5034 patients treated on study, 11% were randomized in the hospital and 13% were greater than 80 years old (median age was 67 years). Patients had long-standing heart failure with a recent heart failure decompensation event, and typically were randomized within one month of the event. Treatment groups were well balanced. A variety of baseline HF standard of care (SOC) therapies and devices were used, including 14% on sacubitril/valsartan at baseline. Of the treated population, 99.5% completed the follow-up for primary endpoints, which were assessed at a median of 10.8 months post-treatment.

Vericiguat was initiated at 2.5 mg and escalated over the course of the study to a target final dose of 10 mg. After one year on treatment, 90% of the patients were at 10 mg.

### Efficacy discussion:

A statistically significant reduction in time to first occurrence of the composite CV death or HF hospitalization primary endpoint was observed (HR 0.90, 95%CI 0.82-0.98,  $p=0.019$ ). Time to first hospitalization, time to total hospitalization, and time to first occurrence of the composite of all cause death or HF hospitalization were statistically significant. Time to CV death and time to all cause death were not statistically significant. Subgroup analyses demonstrated significant interactions for age and for baseline NT-proBNP quartile.

### Safety discussion:

The most common adverse reactions were anemia and dyspepsia. Symptomatic hypotension and syncope occurred more frequently in the vericiguat group.

### Sponsor questions:

1. **Does the Agency agree that the topline efficacy and safety data provided herein from the VICTORIA Phase 3 study are sufficient to support a vericiguat NDA submission?**

U.S. Food and Drug Administration  
Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.gov)

**Meeting Discussion:** The Agency agreed that the presented topline data would support an NDA submission.

**2. Does the Agency have any comments on the following proposed indication for vericiguat at this time?**

***“Vericiguat is indicated (b) (4) chronic heart failure in combination with other HF therapies in adults with EF<45% to reduce the risk of CV death and heart failure hospitalization.”***

**Meeting discussion:** The Agency suggested that the indication of (b) (4) be clarified. The sponsor agreed.

**Additional meeting discussion:** In subgroup analyses, the Agency noted that subjects with the highest baseline NT-proBNP showed the least benefit while subjects with the lowest baseline ejection fraction showed greater treatment benefits. The Agency suggested analyses with NT-proBNP as a continuous variable and analyses based on time from the most recent HF decompensation event. FDA also pointed out that a number of continuous variables had been analyzed dichotomously, and suggested that alternative analyses (e.g., by quartile, continuous) might be more informative.

The Division was interested in analyses by-region use of guideline-directed background pharmacologic and device therapy.

The Division requested the following analyses of efficacy for inclusion in the NDA submission:

- Primary efficacy based on investigator assessment of outcomes.
- Primary efficacy incorporating urgent clinic visits.
- Quality of life outcomes as a function of baseline NYHA class.

With respect to safety, the Division requested utilization of standard MedDRA queries to analyze the occurrence of broad categories of adverse events, for example, syncope, presyncope, loss/alterations of consciousness, dizziness, hypotension, fall, and fractures.

The sponsor plans to submit their NDA in May 2020 and inquired about the possibilities of Breakthrough Therapy Designation (BTD) or receiving priority review. The Agency explained that in principle, a BTD request can be submitted based on phase 3 trial results. The Division emphasized that BTD is not needed to request a priority review.

### **3.0 OTHER IMPORTANT INFORMATION** **PREA REQUIREMENTS**

U.S. Food and Drug Administration  
Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.gov)

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.<sup>1</sup> In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email [Pedsdrugs@fda.hhs.gov](mailto:Pedsdrugs@fda.hhs.gov). For further guidance on pediatric product development, please refer to [FDA.gov](http://FDA.gov).<sup>2</sup>

## **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information<sup>3</sup> and Pregnancy and Lactation Labeling Final Rule<sup>4</sup> websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for

---

<sup>1</sup> When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

<sup>2</sup> <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

<sup>3</sup> <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

<sup>4</sup> <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

#### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

None

#### **5.0 ACTION ITEMS**

None

#### **6.0 ATTACHMENTS AND HANDOUTS**

Sponsor presentation titled: VICTORIA Topline Results MK-1242 (Vericiguat) in Heart Failure with Reduced EF+

U.S. Food and Drug Administration  
Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.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/  
-----

ELLIS F UNGER  
02/21/2020 02:41:22 PM



IND 116743

## MEETING PRELIMINARY COMMENTS

Merck Sharp & Dohme Corp.  
Attention: Tonja Hampton, MD  
Director, Global Regulatory Affairs  
126 E. Lincoln Ave, RY34-B188  
PO Box 2000  
Rahway, NJ 07065

Dear Dr. Hampton:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Vericiguat (MK-1242).

We also refer to your January 6, 2020, correspondence requesting a Pre-NDA meeting to obtain feedback on the content and format of the upcoming NDA submission and related regulatory deliverables.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, please call me at (301) 796-0442.

Sincerely,

*{See appended electronic signature page}*

Alexis Childers, RAC, CQIA  
Sr. Regulatory Project Manager  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation 1  
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**PRELIMINARY MEETING COMMENTS**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** February 20, 2020, 12:30-1:30 pm  
**Meeting Location:** Teleconference

**Application Number:** 116743  
**Product Name:** Vericiguat (MK-1242)  
**Indication:** In combination with other heart failure therapies, (vericiguat) is indicated in adult patients (b) (4) chronic heart failure (HF) with ejection fraction below 45% to reduce the risk of cardiovascular death and heart failure hospitalization.

**Sponsor Name:** Merck Sharp & Dohme Corp.

*Office of Drug Evaluation I, Division of Cardiovascular and Renal Products*

Norman Stockbridge, MD, PhD	Director
Aliza Thompson, MD, MS	Deputy Director
Mary Ross Southworth, PharmD	Deputy Safety Director
Preston Dunnmon, MD	Clinical Reviewer
Elizabeth Hausner, DVM	Pharmacologist
Xuan Chi, MD, PhD	Pharmacology Team Leader
Edward Fromm, RPh, RAC	Chief, Project Management Staff
Alexis Childers, RAC, CQIA	Sr. Regulatory Health Project Manager

*Office of Clinical Pharmacology, Division of Clinical Pharmacology I*

Sudharshan Hariharan, PhD	Clinical Pharmacology Team Leader
Harisudhan Thanukrishnan, PhD	Clinical Pharmacology Reviewer

*Office of Biometrics, Division of Biometrics I*

Jialu Zhang, PhD	Statistical Team Leader
Dali Zhou, PhD	Statistician

*Office of Pharmaceutical Quality*

Mohan Sapru, PhD	Team Leader
Grace Chiou, PhD	Chemist

*Office of Scientific Investigations*

TBD

**SPONSOR ATTENDEES**

**Merck Team**

Joerg Koglin, MD, PhD  
Robert Blaustein, MD, PhD

Mahesh Patel, MD

Gregory Golm, PhD  
Gang Jia, PhD  
Justo Sierra Johnson, MD

Maria Trujillo, PhD

Timothy Johnson, PhD

Rupesh Amin, PhD

Nathalie Toussaint, PhD

Frank Grande, MSc  
Sandip Roy, PhD

Vivian Fuh, MD  
Tonja Hampton, MD  
Lina AlJuburi, PharmD, MS

**Bayer Team**

Richard Nkulikiyinka, MD  
Lothar Roessig, MD  
Vanja Vlajnic  
Nils Konieczny, MD, MHBA  
Corina Becker, PhD

Renate Block  
Regina Seidel

Evelin Amoulong

Robert Kraemer, PhD

Vice President, Global Clinical Development  
Executive Director, Global Clinical Development  
Executive Director, Global Clinical Development  
Executive Director, Biostatistics  
Senior Principal Scientist, Biostatistics  
Senior Principal Scientist, Clinical Safety Risk Management  
Principal Scientist, Quantitative Pharmacology & Pharmacometrics  
Principal Scientist, Safety Assessment & Laboratory Animal Resource  
Distinguished Scientist, Program Development, Safety Assessment & Laboratory Animal Resource  
Associate Director, Global Regulatory Affairs- CMC  
Director, Global Regulatory Affairs - CMC  
Associate Vice President, Global Regulatory Affairs  
Executive Director, Global Regulatory Affairs  
Director, Global Regulatory Affairs  
Director, Global Regulatory Policy

Vice President, Clinical Development  
Global Clinical Leader, Clinical Development  
Study Statistician, Clinical Statistics  
Global Safety Leader  
Clinical Pharmacology Leader, Clinical Pharmacology  
CMC Manager, Regulatory CMC  
Head, Regulatory Strategy, Cardiology & Nephrology  
Global Regulatory Strategist, Regulatory Affairs  
Global Program Head



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

## **Introduction:**

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for February 20, 2020, from 12:30-1:30 pm between Merck Sharp & Dohme Corp. and the Division of Cardiovascular and Renal Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

## **1.0 BACKGROUND**

Vericiguat is a soluble guanylate cyclase (sGC) stimulator being co-developed by Merck and Bayer for the treatment of chronic heart failure (NYHA class II-IV) in adults with reduced left ventricular ejection fraction (LVEF <45%) in addition to standard of care to reduce the risk of cardiovascular death and heart failure hospitalization.

Vericiguat was granted Fast Track Designation in 2014 for the treatment of heart failure with a reduced EF (HFrEF). An EOP2 meeting was held in 2015 after completion of a phase 2b study (Study 15371- SOCRATES-REDUCED). At the meeting, the Division agreed that a single pivotal trial would be sufficient to submit a marketing application with a p-value substantially < 0.05, and the mortality component trending in a positive direction. The global clinical trial called, VeriCiguaT gLObal study in patients with heart failure and Reduced ejection frAction (VICTORIA) commenced in 2016 and concluded in 2019. Topline results were shared at a meeting conducted on February 3, 2020. The trial met its primary endpoint.

Merck requested this meeting to gain feedback from FDA related to the upcoming NDA submission, the content and format of the application, and related regulatory deliverables.

## **2.0 DISCUSSION**

*Note to Sponsor: We have rearranged the order of your questions.*

## 2.1. CMC

### Question 1

Does the Agency agree that the Formal Stability Studies (FSS) and supportive stability studies are adequate to register vericiguat film coated tablets in 14 count HDPE bottles?

**FDA response:** It is our expectation that the NDA will include at least 12 months of long-term stability data and 6 months of accelerated stability data, for each presentation in the intended commercial container closure system, at the time of submission as per ICH QIA(R2). However, based on your supportive data from open-dish studies and (b) (4) modeling, we would accept 9 months of long-term stability data and 6 months of accelerated stability data for the 14-count HDPE presentation at the time of NDA submission, accompanied by a commitment to provide the additional 3-month long-term stability data within three months of NDA submission.

## 2.2. Nonclinical Development

### Question 2

Does the Agency agree that the nonclinical safety package as outlined is adequate to allow review of the NDA to support filing and approval of vericiguat?

**FDA response:**

We agree that the proposed nonclinical safety package is adequate to support NDA filing and review; approvability is a review issue.

*Additional Comment:*

We note cardiac septal defect and truncus arteriosus reported in the 2.5- and 7.5-mg/kg dose groups in your rabbit embryo-fetal development study (Study Number T101194-6). While a dose-response relationship was not apparent, these are fetal anomalies with background rates of less than 1%. As the embryo-fetal development studies are not powered to show dose relationships for rare anomalies, a rare finding such as ventricular septal defects in multiple drug-treated litters is considered a teratogenic effect and should be included in the label (Guidance for Industry: Reproductive and Developmental Toxicities – Integrating Study Results to Assess Concerns (<https://www.fda.gov/media/72231/download>)).

## 2.3. Clinical Pharmacology and Biopharmaceutics

### Question 3

Does the Agency agree that the clinical pharmacology and biopharmaceutics package is sufficient to support the review of the vericiguat NDA?

**FDA response:**

Yes, we agree that the proposed package is sufficient to support NDA review.

We have the following additional requests:

1. When you submit your QT evaluation report, please include a completed version of the “QT Evaluation Report Submission Checklist” located at the IRT website (<https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinary-review-team-cardiac-safety-studies-formerly-qt-irt>).
2. To facilitate the review of the nonclinical study reports, please submit the following information for each experiment:
  - a. Raw and unaltered electrophysiology records (e.g. no baseline subtraction or zeroing of baseline). The file format for the raw electrophysiology records should be in xls, xlsx or xpt format, and contain at a minimum information about time, voltage and current signals (note specific units for these signals). For current clamp experiments, time and voltage as well as stimulus characteristics.
  - b. An overview file, e.g. in xls, xlsx, xpt or txt, describing the experimental conditions for each of the raw electrophysiology records. The description should include at a minimum the name of the file, temperature of the recording, when drugs and at what concentrations were added, and other information relevant to interpret the results.

## 2.4. Multidisciplinary

### Question 4

Does the Agency agree with the proposed content and format of the draft table of contents (TOCs) for the vericiguat NDA submission?

**FDA response:**

The proposed content and format of the draft TOCs seem reasonable.

### Question 5

Does the Agency agree with the scope and high-level content of the Analysis Package described in the Background Package to support review of the vericiguat NDA?

**FDA response:**

Yes.

### Question 6

Does the Agency concur that the results provided from the VICTORIA study are compelling and support “Breakthrough Designation” criteria for vericiguat?

**FDA response:**

At our meeting on February 3, 2020, we discussed the criteria for Breakthrough Therapy Designation (BTD) and our concerns with the VICTORIA study as it relates to satisfying these criteria. If you desire further comment from the Division as to the appropriateness of BTD, you should submit a Preliminary Breakthrough Therapy Designation Request (BTDR) Advice form to the IND.

**Question 7**

Does the Agency agree that the results provided from the VICTORIA study meet the criteria for Priority Review for vericiguat?

**FDA response:**

Based on the information provided thus far, Priority Review is possible, though this will be determined at the time of NDA filing.

**Question 8**

Does the Agency agree with the Sponsor's proposed format for submission of information requested by the Office of Scientific Investigation (OSI) to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments and the background packages for these inspections?

**FDA response:**

Yes, we agree. For further information on what to include for these items, please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

**Question 9**

Does the Agency concur that the list of trials for which we will provide financial disclosure information is acceptable? If the Agency desires financial disclosure information for any other trials, please identify the trials.

**FDA response:**

We agree that only the VICTORIA phase 3 trial requires financial disclosure information. This information should include the following summary information in addition to specific datasets and forms:

- A dataset of the clinical sites, clinical investigators, and sub-investigators
- The total number of investigators and sub-investigators
- The number of investigators who are Sponsor employees (including both full-time and part-time employees)
- The number of investigators with disclosable financial interests/arrangements (Form FDA 3455)
- If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):
  - Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study
  - Significant payments of other sorts
  - Proprietary interest in the product tested held by investigator
  - Significant equity interest held by investigator in Sponsor
  - Sponsor of covered study (provide details)
  - A description of the steps taken to minimize potential bias
- The number of investigators with certification of due diligence (Form FDA 3454, box 3)
  - An attachment with the reason(s) for certifications of due diligence.

**Additional FDA requests:**

1. Based on the response to question #2 about findings from the embryo-fetal development studies, include a proposal for adequate risk mitigation for the risk of embryo-fetal toxicity (e.g., labeling) along with justification for your approach in your NDA submission. Pharmacovigilance activities to monitor for the risk should also be considered and proposed, as appropriate.
2. From the information that you have submitted, we note that the pre-specified tier-1 combination of adverse events (syncope and symptomatic hypotension) occurred significantly more frequently in the active treatment arm of VICTORIA. However, it is unclear if the occurrence of symptomatic hypotension may have been underestimated by an overly-restrictive definition set that may not have captured other manifestations of hypotension (e.g. presyncope, loss of consciousness, dizziness, falls, and fractures). In this regard, it will be important for you to analyze the differential occurrence of a combination of these events between the treatment arms based on standard MedDRA preferred term sets to identify all adverse events that may fall into any of the following broad categories:
  - Syncope
  - Presyncope
  - Loss/alterations of Consciousness

- Dizziness (postural or not)
- Hypotension
- Falls and fractures.

### **3.0 OTHER IMPORTANT INFORMATION**

#### **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

If, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.<sup>1</sup>

#### **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information<sup>2</sup> and Pregnancy and Lactation Labeling Final Rule<sup>3</sup> websites, which include:

---

<sup>1</sup> <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>

<sup>2</sup> <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

<sup>3</sup> <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

### **ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential

evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.<sup>4</sup>

## **MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

<sup>4</sup> We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

**OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS**

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.<sup>5</sup>

---

<sup>5</sup> <https://www.fda.gov/media/85061/download>

-----  
**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/  
-----

ALEXIS T CHILDERS  
02/18/2020 07:40:39 AM



IND 116743

**MEETING REQUEST-  
WRITTEN RESPONSES**

Merck Sharp & Dohme Corp.  
Attention: Tonja Hampton, MD  
Director, Global Regulatory Affairs  
126 E. Lincoln Ave, RY34-B188  
PO Box 2000  
Rahway, NJ 07065

Dear Dr. Hampton:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Vericiguat (MK-1242).

We also refer to your submission dated March 26, 2019, containing a meeting request. The purpose of the requested meeting was to obtain feedback on the Study Data Standardization Plan (SDSP), and the pooling strategy for efficacy and safety in support of application submission activities.

Further reference is made to our Meeting Granted letter dated March 27, 2019 wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your April 15, 2019 background package.

If you have any questions, please call Alexis Childers, Sr. Regulatory Project Manager at (301) 796-0442.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure: Written Responses



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

## WRITTEN RESPONSES

**Meeting Type:** C  
**Meeting Category:** Guidance

**Application Number:** 116743

**Product Name:** Vericiguat (MK-1242)  
**Indication:** treatment of chronic heart failure (NYHA class II-IV) in adults with reduced left ventricular ejection fraction to reduce the risk of cardiovascular death and heart failure hospitalization

**Sponsor Name:** Merck Sharp & Dohme Corp.  
**Regulatory Pathway:** 505(b)(1)

### 1.0 BACKGROUND

Vericiguat is a soluble guanylate cyclase (sGC) stimulator being co-developed by Merck and Bayer for the treatment of chronic heart failure (NYHA class II-IV) in adults with reduced left ventricular ejection fraction (LVEF <45%) in addition to standard of care to reduce the risk of cardiovascular death and heart failure hospitalization.

Vericiguat was granted Fast Track Designation in 2014 for HF<sub>r</sub>EF. An EOP2 meeting was held in 2015 after completion of a phase 2b study (Study 15371- SOCRATES-REDUCED). At the meeting, the Division agreed that a single pivotal trial would be sufficient to submit a marketing application with a p-value substantially < 0.05, and the mortality component trending in a positive direction. The global clinical trial titled VeriCiguaT glObal study in patients with heart failure and Reduced ejection fraction (VICTORIA) is an event-driven trial. The study commenced in 2016 and randomization closed on December 21, 2018. In a 1:1 randomization scheme, 5050 patients are being evaluated with vericiguat 10 mg target dose arm (starting dose 2.5 mg) vs. matching placebo arm. The primary endpoint is time to the first occurrence of the composite of HF hospitalization or CV death. The sponsor plans to submit an NDA based on this single pivotal trial and requested feedback on submission related activities.

### 2.0 QUESTIONS AND RESPONSES

1. Does the Agency concur with the Sponsor's Study Data Standardization Plan (SDSP) for vericiguat?

**FDA response:** For VICTORIA, please use the WHO Drug Dictionary instead of the Merck Drug Dictionary. Otherwise, your Study Data Standardization Plan (SDSP) is acceptable.

2. Does the Agency agree with the proposal to not pool safety and efficacy data from the Phase 2 SOCRATES trials with data from VICTORIA?

**FDA response:** Yes, we agree. Please note that analysis of the two SOCRATES trials needs to be stratified by trial if they are combined.

3. As the Sponsor anticipates that we will be able to describe sufficiently all data supporting the effectiveness of vericiguat in patients with HFrEF within the Summary of Clinical Efficacy (Module 2.7.3), does the Agency agree that the Summary of Clinical Efficacy can serve as the Integrated Summary of Effectiveness (ISE), and submission of an ISE (Module 5.3.5.3) will not be required?

**FDA response:** Yes, we agree.

### **Additional Requests from the Agency**

1. Please submit the following information at the time of NDA submission:

- a. Protocol and Statistical Analysis Plan

1. all versions of the protocol for VICTORIA and the date when changes were implemented. Include a Summary of Changes for each version.
2. all versions of the Statistical Analysis Plan (SAP) for VICTORIA. Include a Summary of Changes for each version and the number of subjects enrolled in the trial at the time the change was made.

- b. Clinical Trial Materials

- 1) case report forms (CRFs) and narratives for all subjects who died, dropped out, discontinued study drug for any reason, experienced a serious adverse event (SAE), or reached an efficacy endpoint. Please note that CRFs must include all clinical documents collected regardless of whether you label them as "CRFs" (Medwatch forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.).
- 2) sample clinical trial kits, from both treatment arms, identical to those used during VICTORIA. Ship them to Alexis Childers' desk address in the same packaging as will be used for shipping to investigative sites.

- 3) all data management plans. Cite all amendments for each data management plan, including all manual and programmatic checks.
- 4) site monitoring plan and all amendments with applicable dates for VICTORIA. If changes to your site monitoring plans were not documented contemporaneously by formal signed amendments, explain the amendment process.
- 5) a description of the responsibilities of each academic research organization (ARO) or clinical research organization (CRO) used in VICTORIA.
- 6) all charters for committees involved in conducting VICTORIA (e.g., Data Safety Monitoring Board [DSMB], Steering Committee, etc.)
- 7) all meeting minutes of all groups with any responsibility for the management of the trial, e.g., Executive Committee, Clinical Endpoint Committee, Steering Committee and DSMB. Include agendas and all data/slides presented to the Committee. Indicate whether the meeting was opened or closed. For those meetings that were cancelled or meetings where no minutes were taken, include a place holder for that meeting noting such and signed by a member of the clinical team. Ensure that these packages include a table of contents and are bookmarked by date.
- 8) all newsletters and all other communications to investigational sites and national coordinators from the group(s) responsible for the conduct of your trials. Please bookmark the newsletters by date.

c. General Data and Analyses

- 1) all code and datasets used to create your analyses found in the main sections of your Summary of Clinical Efficacy, Summary of Clinical Safety, and Phase 3 trial clinical study report. If code contains a macro, include the macro code.
- 2) Footnote the tables and figures featured in the main clinical efficacy and safety sections of the NDA with the name of the code used to create the table or figure.
- 3) all scripts/programs used to create the analysis datasets for all derived datasets used in your key analyses. The scripts and define files should be sufficient to facilitate understanding of how the analysis datasets were created. If variables are inadequately described in the define files, you may need to also submit all datasets (and associated define files) used to derive your analysis datasets. Paginate all define files and submit as pdfs.

- 4) list of datasets that you assert are of high quality for review. Explain how you assessed the quality of your datasets and what you did to ensure your datasets are suitable for an NDA review. Submit code that was used to create or clean up your analyses datasets.
- 5) Kaplan-Meier time to event analysis datasets and code (both safety and efficacy) censoring subjects without an event at the date of last known information about the event of interest (not vital status check at the end of the study). Indicate how censoring was determined (e.g., by a patient visit or by telephone call). This dataset should allow one to analyze by intent-to-treat (ITT) as well as on-treatment. The events should include all adjudicated events, any important composite endpoints, important adverse events, and laboratory parameter changes of interest.
- 6) subject ID variable for all open label extension study datasets that links the subject to the ID used in the pivotal trial datasets.
- 7) dataset that contains all subjects that were unblinded. Include the unique subject ID, the treatment received, who requested unblinding, date of unblinding, and the reason for unblinding.
- 8) dataset that contains a list of all subjects for whom you submitted a CRF, narrative, or adjudication packages. The dataset should contain four variables with an indicator for whether each item was submitted.
- 9) one table which includes the following information for the pivotal study(ies):
  - Dates of first patient and last patient visits
  - Dates of data lock
  - Dates for each interim analysis
  - Dates of all versions of the SAP (with a hyperlink to each SAP)
  - Dates of the initial protocol and all revisions. (with a hyperlink to the protocol and each revision).

e. Important Endpoints

- 1) an adjudication dataset that contains one line per event. The columns in the dataset should include the study number, unique subject id, randomized treatment, actual treatment, flag that indicates subject is included in the ITT analysis, flag that indicates the subject is included in the safety analysis, the event type being adjudicated (i.e., stroke, major bleed, death, hospitalization for heart failure, etc.), date of event, what triggered the event for adjudication (i.e., investigator, laboratory result, etc.), the investigator's assessment of the event, each adjudicators' result (in chronological order across the dataset), date of each adjudication, final adjudication result and date.

- 2) a comprehensive description of the algorithm used to identify potential endpoint events in your final clinical study report. If your algorithm changed, you should also provide detailed information on its evolution, including when and why changes were made.

### Other

- 1) statement of Good Clinical Practice confirming that all clinical studies were conducted under the supervision of an Institutional Review Board and with adequate informed consent procedures. If you were granted an IRB Waiver during this trial because a specific site or country operated under a Central Ethics Committee (CEC) and/or Local Ethics Committees (EC) which we agreed maintain the same oversight responsibilities as IRBs, please reference the waiver and include the date.
- 2) rationale for assuring the applicability of foreign data to U.S. population/practice of medicine in the submission for those phase 3 trials conducted primarily outside of the United States (OUS)

There are two major pieces to this applicability of foreign data issue as follows:

- Are the patients the same (US versus rest of the world)?
  - Are the medical systems treating the disease the same way with respect to interventions and background therapy on a region-specific basis?
- 3) Response to an information request from the Office of Scientific Investigations. This document includes data requests that are to be addressed in your initial submission.
  - 4) an annotated version of these pre-NDA meeting minutes that include a hyperlink, when applicable, to the analysis and/or documents requested. This document can be placed in the reviewer's aid.

## **3.0 OTHER IMPORTANT INFORMATION**

### **DATA STANDARDS FOR STUDIES**

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

**U.S. Food and Drug Administration**  
Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.gov)

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team ([cdcr-edata@fda.hhs.gov](mailto:cdcr-edata@fda.hhs.gov)) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The [FDA Study Data Technical Conformance Guide](#) (Section 7.2 eCTD Sample Submission pg.

30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the [FDA Study Data Standards Resources](#) web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

### **DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS**

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

### **OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS**

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

-----  
**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/  
-----

NORMAN L STOCKBRIDGE  
06/01/2019 05:41:39 AM



IND 116743

**MEETING MINUTES**

Bayer HealthCare Pharmaceuticals, Inc.  
Attention: Jin Cho, MS, RAC  
Assistant Director, Global Regulatory Affairs  
PO Box 0915, Bldg. 200, 3rd Fl.  
Whippany, NJ 07981-0915

Dear Mr. Cho:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Vericiguat, BAY 1021189 (sGC Stimulator).

We also refer to the meeting between representatives of your firm and the FDA on November 18, 2015. The purpose of the meeting was to discuss the development plan for Vericiguat.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Alexis Childers, Sr. Regulatory Project Manager at (301) 796-0442.

Sincerely,

*{See appended electronic signature page}*

Ellis F. Unger, M.D.  
Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** EOP2

**Meeting Date and Time:** November 18, 2015, 11:30-1:00 pm  
**Meeting Location:** White Oak Building 22, Conference Room 1419

**Application Number:** 116743  
**Product Name:** Vericiguat, BAY 1021189 (sGC Stimulator).  
**Indication:** to reduce the risk of cardiovascular death and heart failure hospitalization in patients with chronic heart failure (NYHA class II-IV) and reduced left ventricular ejection fraction (LVEF <45%) on top of standard of care (SOC).

**Sponsor Name:** Bayer HealthCare Pharmaceuticals, Inc.

**Meeting Chair:** Ellis F. Unger, M.D.  
**Meeting Recorder:** Alexis Childers

**FDA ATTENDEES**

**FDA ATTENDEES**

*\*Office of Drug Evaluation I*

Ellis Unger, MD,	Director
Robert Temple, MD	Deputy Director
<i>*Division of Cardiovascular and Renal Products</i>	
Norman Stockbridge, MD, PhD	Director
Stephen Grant, MD	Deputy Director
Martin Rose, MD, JD	Clinical Team Leader
Preston Dunnmon, MD	Clinical Reviewer
Thomas Papoian, PhD	Pharm/Tox Team Leader
Elizabeth Hausner, DVM	Pharm/Tox Reviewer
Alexis Childers, RAC	Regulatory Health Project Manager
Michael Monteleone, MS, RAC	Associate Director for Labeling
Mary Ross Southworth	Deputy Safety Director

*\*Office of Clinical Pharmacology*

Martina Sahre, PhD	Clinical Pharmacology Reviewer
Rajanikanth Madabushi, Ph.D.	Clinical Pharmacology Team Leader

*\*Office of Biostatistics, Division of Biometrics I*

Fanhui Kong, Ph.D.	Statistician
Hsien Ming James Hung	Director

## **SPONSOR ATTENDEES**

### ***Bayer***

Koichi Nishijo, MD, PhD	Global Program Head, Global Project Management
Nancy Cook Bruns, MD	Vice President, Head Cardiovascular Group
Lothar Roessig, MD	Global Clinical Leader, Global Clinical Development
Stefanie Lindemann, MD	Global Clinical Leader, Global Clinical Development
Katharina Mueller	Project Statistician, Global R&D Statistics
Corina Becker, PhD	Clinical Pharmacology Leader, Global Clinical Pharmacology
Volker Geiss, PhD	Head of Experimental Toxicology
Regina Seidel Head,	General Medicine III, Global Regulatory Affairs
Frank Broecker, PhD	Global Regulatory Strategist, Global Regulatory Affairs
Jin Cho, MS, RAC	Global Regulatory Strategist, Global Regulatory Affairs

### ***Merck***

Joerg Koglin, MD, PhD	Executive Director, Global Clinical Development
Harold Bernstein, MD, PhD	Director, Global Clinical Development
Bruce Binkowitz, PhD	Executive Director, Biostatistics
Jeffrey Tucker, MD	Executive Director, Global Regulatory Affairs
Scott Hambaugh, MBA	Director, Global Regulatory Affairs

## **1.0 BACKGROUND**

Vericiguat is a soluble guanylate cyclase (sGC) stimulator being developed by Bayer HealthCare Pharmaceuticals, Inc. to reduce the risk of cardiovascular death and heart failure hospitalization in patients with chronic heart failure (NYHA Class II-IV) and reduced left ventricular ejection fraction (LVEF <45%) on top of standard of care.

Under the clinical development program extensive CMC and nonclinical studies have been conducted. According to the sponsor, vericiguat is non-genotoxic, and the nonclinical safety testing did not reveal any critical test substance-related findings for the intended clinical use.

For the clinical program, 18 phase 1 studies have been completed with two additional phase 1 studies being evaluated. The AE profile is associated with its mode of actions, relaxation of smooth muscles leading to vasodilation.

There are two phase 2b studies (Study 15371- SOCRATES, in patients with heart failure and reduced ejection fraction [HFrEF], and Study 15829- SOCRATES HFpEF, patients with heart failure and preserved ejection fraction). Study 15371 has been completed, and Study 15829 will be available in Q1 2016.

Previously, the sponsor had planned for two phase 3 trials, one for subjects with HFREF, and one for subjects with HFpEF. Both were proposed as randomized parallel-group, placebo-controlled, double-blind, event-driven, multi-center clinical outcome trials in patients with chronic heart failure and recent decompensation defined by hospitalization or IV diuretic treatment for heart failure with initiation of treatment within 6 months after clinical stabilization.

The sponsor would like to discuss the all aspects of clinical development, and specifically a strategic change targeting approval based on a single phase 3 study VICTORIA, in patients with heart failure and reduced ejection fraction.

## 2.0 DISCUSSION

### 2.1 CMC

#### **Drug substance** (*Requesting Written Feedbacks Only for Question 1 and 2*)

1. The sponsors propose to use [REDACTED] <sup>(b) (4)</sup> substance as starting material in the synthesis of vericiguat for a NDA/MAA submission. Does the Agency agree?

**FDA response:** We agree with your proposal to designate [REDACTED] <sup>(b) (4)</sup> as starting material. Your NDA should include the following items:

- Complete name and address of the intended vendor of the proposed starting material.
- Purging studies to demonstrate that the proposed starting material and its impurities will not be present at levels greater than [REDACTED] <sup>(b) (4)</sup> % in the drug substance provided these compounds are not structural alerts for genotoxicity.
- Appropriate controls of the proposed starting materials using validated analytical test methods to separate and measure potential impurities.
- In-house acceptance criteria and Vendor's Certificate of Analysis.
- Synthetic scheme and method of manufacture.
- Impurity profile.
- Thorough discussion of potential carry-over of impurities present in the starting materials to the final drug substance.
- A description of the analytical methodology used for the drug substance that is capable of resolving and quantifying impurities carried over from the proposed starting materials as well as any process impurities.
- Change control strategies for any potential revisions to the manufacture of the proposed starting materials, including the proposed procedures for the vendor's reporting of any changes in starting material manufacture.
- Supportive literature data, if available

**Discussion during meeting:** No further discussion.

2. The sponsors propose to use [REDACTED] <sup>(b) (4)</sup> and [REDACTED] <sup>(b) (4)</sup> as raw materials in the synthesis of vericiguat for the NDA/MAA submission. Does the Agency agree?

**FDA response:** We agree.

**Discussion during meeting:** No further discussion.

## 2.2 NON-CLINICAL DEVELOPMENT

3. Does the Agency agree that the completed and proposed non-clinical studies described are adequate to support the NDA/MAA for vericiguat in the proposed indication?

**FDA response:**

1. In general, we agree with the scope of the studies completed and proposed.
2. Please provide an update on the status of characterizing the insoluble urinary crystals.
3. Please provide an update on the status of determining whether the impurity or the drug substance caused the equivocal positive result in the micronucleus assay.

**Discussion during meeting:** No further discussion.

**Post-meeting note:** Please provide the full and complete report for the vericiguat-nitroglycerin study conducted in dogs (referenced on slide 12 of your presentation).

## 2.3 CLINICAL DEVELOPMENT

### 2.3.1 CLINICAL PHARMACOLOGY

- 4 Does the Agency agree that the completed, ongoing and proposed clinical pharmacology studies described are adequate to support NDA/MAA for vericiguat in the proposed indication?

**FDA response:** Based on the information submitted, the clinical development program should be adequate. It may be useful to conduct a sacubitril/valsartan pharmacodynamic interaction study prior to the start of phase 3.

**Discussion during meeting:** Bayer indicated that they plan to conduct the requested study in 2016. Preclinical studies of administering verciguat with valsartan/sacubitril did not suggest more than an additive effect on arterial blood pressure (refer to attached slides). Hence Bayer believes that there is no reason to be concerned about additional risk in sequentially adding one drug to the other, and the phase 3 trial can safely begin before the interaction study is completed. They stated that initial data from the interaction study will be available around June 2016 and they plan to start phase 3 in June 2016.

The Division stated that the potential for hypotension with concomitant medications, specifically sacubitril/valsartan, should be disclosed in the informed consent and discussed with the DSMB. The sponsor agreed.

The Division also expressed concern over the safety of concomitant administration of nitroglycerin based on the experience in the riociguat development program. Co-administration of nitroglycerin within 4 hours of riociguat resulted in loss of consciousness and so use of nitroglycerin with riociguat is contraindicated. The DSMB should be made aware of the concern for this interaction (see also the response to and discussion of question 13 below).

The Division also indicated concern about approvability if subjects are not on US standard of care, including sacubitril/valsartan and ICDs at baseline. The sponsor stated they will enroll a high proportion of patients from the US.

- 5 Does the Agency agree that based on the available data a thorough QT study is not required for the NDA/MAA for vericiguat in the proposed indication?

**FDA response:** Assuming that the QTc/concentration evaluation from your phase 1 program shows no relationship, and the upper limit of the 90% CI for the change in QTc in the highest quartile of exposure from your phase 2 and phase 3 studies is below 10 ms, a TQT study may not be necessary.

**Discussion during meeting:** Bayer stated that they cannot conduct a TQT study at doses 3-5 times the therapeutic dose as recommended in ICH E14 because doses that high are not tolerable. ECG data were collected in the phase 2b study and a signal for QT prolongation was not seen; therefore, Bayer does not plan to do a QT evaluation in phase 3.

The Division is aware of the dosing limitations of sGC stimulators because the issue was the same for the riociguat program. The Division expects that a similar approach to TQT evaluation will be taken for vericiguat as was done for riociguat, whereby ECG data from pivotal trial 12934 (PATENT-1) were augmented with moxifloxacin data from study 13796 (A randomized, double-blind, 2-way crossover, placebo-controlled study to investigate the influence of a single-dose of moxifloxacin on the QTc interval in healthy male and female subjects for positive control validation in selected centers of the PATENT-1 trial).

## 2.3.2 CLINICAL

### Vericiguat dose in proposed Phase III study

- 6 Based on the Phase I and Phase IIb results provided, does the Agency agree that once daily vericiguat titrated up to 10 mg is an acceptable target dose for the pivotal Phase III study?

**FDA response:** The information provided does not show a clear exposure-response based on NT-proBNP or other markers such as systolic blood pressure or heart rate. Therefore, it is not possible for us answer your question.

**Discussion during meeting:** Bayer disagreed with the Division stating that regression analysis indicates a dose relationship (see attached slides 8-10) and so feel they have a found a suitable dose for phase 3.

The Division agreed that the dose proposed is reasonably safe but recommended that a higher dose be studied if possible. The relationship between a modest effect on NT-proBNP and morbidity and mortality is unknown. Given this uncertainty, the Division stated that studying a higher dose would be prudent to increase the chance of identifying an efficacious dose. The Division stated Bayer could incorporate an arm in which patients are titrated to the highest dose tolerable to allow higher doses to be studied. It is also possible to perform the primary analysis on the pooled outcomes of subjects randomized to both arms of verciguat as compared to subjects randomized to placebo.

Postmeeting note: For Tables 9-22 and 9-23, in the Briefing document, please provide the incidence of “vascular disorders” and “hypotension” in the following format:

Dose Group	Step 1 V1 to V2	Step 2 V2 to V3	Step 3 V3 + 2 weeks	V3 + 2 weeks to end of treatment (V5)
Placebo	n (%)			
1.25 mg				
2.5 mg				
2.5 – 5 mg				
2.5 – 10 mg				

### **Study endpoints in proposed Phase III study**

- 7 Does the agency agree to the primary composite efficacy endpoint: time to CV death and first HF hospitalization?

**FDA response:** We agree.

**Discussion during meeting:** No further discussion.

- 8 Does the agency agree to the secondary endpoints?

**FDA response:** If you seek labeling that includes secondary endpoints, you will need to control Type-I error rates and plan a sequential analysis. These could include the components of the primary endpoint, but such components would already be displaying in labeling. Time to all-cause mortality is an analysis of interest. But a statistically positive result would not result in an all-cause mortality claim, given that all-cause mortality results will be driven by cardiovascular mortality in this population. We believe that a frequency analysis for HF hospitalization is problematic for two reasons: the results of this analysis will likely be driven by first events, and this analysis treats three 1-day admissions as somehow worse than a single 4-month admission. We think a more relevant outcome for secondary analysis would be days alive and out of hospital.

**Discussion during meeting:** No further discussion.

### **Standard of care**

9 Does the agency agree to the definition/use of standard of care?

**FDA response:** The Division has two concerns regarding background therapies:

- Regarding background pharmacologic therapies for HFrEF, the standard of care for class II/III HFrEF subjects can reasonably be expected to be changing in the coming years with the recent approval of sacubitril/valsartan in the United States. To a lesser degree, the same may be true for the incorporation of ivabradine into clinical practice for those subjects who cannot tolerate guideline-defined dose targets for beta-blockers who meet resting pulse rate treatment criteria. The adoption of these new therapies into clinical practice may differ markedly across regions.
- Recent clinical trials have demonstrated a remarkable variation in the use of indicated device therapies for HFrEF, specifically the ICD, CRT, and CRT-D, all of which impact mortality and/or hospitalization for worsening heart failure in an important way.

It will therefore be important that life-saving background pharmacologic therapies not be dose-reduced or withdrawn for the sake of initiating or dose escalating vericiguat, and that documentation that background pharmacotherapies have been optimized (or the reasons why they have not been) be protocol-driven and analyzable from the eCRF. For both background pharmacologic and device therapies for HFrEF, it will be important that the utilization of these therapies reflect contemporary management of HFrEF in US heart failure centers, and that benefit of vericiguat is demonstrated in that setting.

**Discussion during meeting:** No further discussion.

10 As the standard of care for the treatment of HFrEF patients is evolving, the sponsors intend to include patients utilizing new heart failure medication in the Phase III. Based on this concept, does the Agency support the concomitant administration of sacubitril/valsartan plus vericiguat upon approval?

**FDA response:** It will be important that the safety and effectiveness of vericiguat administration on a background of sacubitril/valsartan be unequivocally defined, given that the use of the latter can be reasonably expected to increase in the future. A dedicated drug-drug PD interaction study examining effects on blood pressure could be helpful in this regard.

**Discussion during meeting:** See discussion under question 4.

### **Study design and patient selection**

11 Does the Agency agree that the proposed single pivotal HFrEF Phase III study as described in the briefing package is adequate to support a NDA/MAA application and to obtain approval of vericiguat?

**FDA response:** For a single trial approval, the p-value for the primary efficacy outcome that you propose should be substantially less than 0.05, with the mortality component at least trending in the direction of benefit.

**Discussion during meeting:** No further discussion.

- 12 Does the Agency agree that the proposed HFREF Phase III study as described in the briefing package is adequate to support a NDA/MAA application of vericiguat in the proposed indication considering the enrichment criteria?

**FDA response:** This will depend on the outcome of the trial with respect to baseline levels of NT-proBNP (e.g. median and quartile analyses). If there is no relationship demonstrated, a more general indication not based on NT-proBNP would be supported.

**Discussion during meeting:** Bayer asked if heart failure decompensation within the prior 6 months is acceptable as a prognostic enrichment factor and if used, whether it would limit the target patient population in labeling to those with decompensation within the past 6 months. The Division has no *a priori* objection to Bayer's plan. Prognostic enrichment may or may not lead to specific identification of the enriched group in labeling. Whether a broader claim would be granted would depend on whether analyses suggest that efficacy is importantly different in those who are the more severely ill/symptomatic.

- 13 Does the agency agree to the following inclusion and exclusion criteria?

**FDA response:** The inclusion criteria seem reasonable, though you should consider capping the number of New York Heart Association functional class II subjects enrolled, particularly if an over-enrollment of these subjects would reduce the event rate of primary outcomes below that which is anticipated. Occurrences of the composite efficacy outcome and its components should be assessed based on categories of baseline LVEF, and as noted above, device utilization in those with an LVEF  $\leq 35\%$  should reflect contemporary US practice.

With respect to the exclusion criteria, we do not understand the rationale for excluding the current or anticipated use of long-acting nitrates only, as opposed to all nitrates. For riociguat, based on drug-drug interaction studies, the administration of nitrate donors in any form, and specifically nitroglycerin, is contraindicated in labeling due to hypotension resulting in syncope as follows:

*Nitrates:* Riociguat 2.5 mg tablets potentiated the blood pressure lowering effect of sublingual nitroglycerin (0.4 mg) taken 4 and 8 hours after riociguat. Syncope was reported in some patients [see *Contraindications (4.2)*].

At least 2/3 of the HFREF population will have coronary artery disease as the etiology of their heart failure in the trial you propose, many of whom may carry and in fact use sublingual nitroglycerin from time to time for chest pain. Assuming that vericiguat carries this same contraindication, please explain how you are going to instruct these patients on the safe use of nitroglycerin in the event they require this to abort an episode of angina.

We note that you have an ongoing DDI study in progress assessing the PD effects of concomitant administration of nitroglycerin and vericiguat. These data will be central to the safety profile of vericiguat use in HFrEF subjects with important coronary artery disease.

The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for African-American patients with NYHA class III–IV HFrEF receiving optimal therapy. Such patients, unless the combination is contraindicated or they have demonstrated intolerance to it, should not be enrolled in your development program, and therefore will not be candidates for this therapy in clinical practice.

**Discussion during meeting:** Bayer indicated that they were conducting studies of nitrate interaction. A DDI study in dogs showed only additive, as opposed to synergistic, effects (slide 12 of 14). A DDI study of nitroglycerin in healthy volunteers has been completed recently with preliminary data suggesting that co-administration of nitroglycerin is safe and well tolerated at vericiguat  $T_{max}$ . Based on this preliminary information, Bayer believes use of short-acting nitrates is safe and should be allowed in the Phase 3 HFrEF trial (VICTORIA), though long-acting nitrate use will not be allowed.

The sponsor reports that two additional nitrate DDI studies are planned (per slide 12/14):

- DDI Study of Vericiguat/nitroglycerin in stable CAD pts, protocol approved, enrollment ongoing
- DDI study of vericiguat/long-acting nitrates planned after analysis of data about short acting nitrates, in parallel to Phase 3.

The Division stated that because Bayer will not have completed the vericiguat-nitrate DDI study in CAD subjects before VICTORIA begins, both the Investigator Brochure and Informed Consent needs to disclose a concern for a nitrate interaction. The DSMB should be aware of the possibility of serious AEs. You should also disclose that you discontinued the PATENT-PLUS trial in which the combination of riociguat + sildenafil was studied because half the subjects dropped out for adverse events related to hypotension.

The Division also believes ascertainment of adverse events possibly caused by an interaction between vericiguat and nitroglycerin should not be left solely to spontaneous adverse event reporting, but should be protocol-driven with eCRF checkboxes for syncope, pre-syncope, and loss of consciousness with capture of antecedent nitrate use. Bayer indicated that they plan to provide specific recommendations on nitrate use and its effects in the protocol. The Division requested submission of the eCRF for review prior to study start.

**Post Meeting Note:** Given that at least 2/3 of the subjects in your Phase 3 HFrEF trial will have coronary artery disease as the basis for their CHF and will likely be carrying nitroglycerin for prophylaxis and treatment of angina attacks, we continue to believe that running your ongoing nitrate DDI studies in parallel to your Phase 3 trial (as opposed to getting the nitrate DDI data in CAD subjects first) is suboptimal. We point out that your

nitrate interaction study and PATENT-PLUS study in the riociguat program directly impacted the inclusion/exclusion criteria for the phase 3 trials that followed.

14 Does the agency agree to the study design?

**FDA response:** Please see our comments above regarding the statistical implications of a single trial approval and the inclusion/exclusion criteria you propose.

**Discussion during meeting:** No further discussion.

15 Does the agency agree on the protocol procedures associated with patients within the lower BP range  $100 < 110$  mm Hg?

**FDA response:** These subjects were not assessed in SOCRATES-reduced, and so it is unclear if the safety experience from that study will apply going forward to a population with lower baseline systolic blood pressures. The safety of these subjects should be a focus of ongoing DSMB review.

**Discussion during meeting:** No further discussion.

**Study design and patient selection: Does the Agency agree to the statistical assumptions for the Phase III (HFREF) study?**

**FDA Response:** If the statistical assumptions for the study, e.g., proportional hazard assumption, are violated, the power for detecting the treatment efficacy of the vericiguat versus placebo may be compromised. If the assumption of non-informative censoring is violated, then biases may be introduced. Accordingly, we suggest that you conduct sensitivity analyses regarding these assumptions.

**Discussion during meeting:** No further discussion.

16 Does the Agency agree with the proposed statistical analysis of the primary efficacy endpoint?

**FDA response:** Since the p-value for the primary efficacy analysis needs to be substantially less than 0.05 for the drug to be approvable, the nominal significance levels at the interim analysis and the final analysis need to be adjusted accordingly.

**Discussion during meeting:** Bayer asked for clarification. The Division explained that if all the first events are hospitalizations, then  $p \leq 0.01$  may be necessary for approval. The concern is that a very large portion of alpha (i.e., 0.01) may be spent at the interim (depending on the correlation between hospitalization events and mortal events) and so not enough alpha will remain for the primary analysis when the trial is completed. Internal Agency discussion ensued and agreement on this issue has not yet been reached.

**Post meeting note:** Internal discussion is still ongoing. A separate letter will be provided in follow up to the meeting minutes.

17 Does the Agency agree with the proposed testing procedures for the secondary endpoints?

**FDA response:** You propose as secondary endpoints components of the primary endpoint (time to first HF hospitalization and time to cardiovascular death) in one family, and, in a second family, time to recurrent HF hospitalization and time to mortality of any cause. No aspect of this plan seems efficient. If the study is successful on the composite, your claim will be restricted to components of the primary endpoint that trend favorably. Thus, it is not necessary to include them as secondary endpoints in an alpha-conserving strategy. Recurrent hospitalization is closely related to first hospitalization, so it would not lead to an independent claim worthy of alpha allocation. (b) (4)

**Discussion during meeting:** No further discussion.

18 Does the Agency agree with the predefined stratification and subgroup analysis strategy?

**FDA response:** The stratification scheme is acceptable. However, the stratification factors may need to be incorporated in the statistical analyses accordingly.

**Discussion during meeting:** No further discussion.

19 Does the Agency agree with the methodology proposed to minimize missing data and the approach for handling missing data?

**FDA response:** This is acceptable.

**Discussion during meeting:** No further discussion.

20 Does the Agency agree with the proposed sample size calculation?

**FDA response:** The sample size seems to be large enough to achieve the power of the test for the current alpha level of 0.05. However, given the required alpha level is smaller than that, the sample size needs to be adjusted accordingly.

**Discussion during meeting:** No further discussion.

21 Does the Agency agree with the proposed details of the planned interim analysis and size estimation?

**FDA response:** See responses to Questions 16 and 20.

**Discussion during meeting:** See discussion under question 16.

- 22 Based on the proposed exclusion criteria for the Phase III study, the sponsors believe approximately 200-250 African-American or Black patients will be enrolled in the study. Does the Agency agree that the proposed African-American or Black cohort in Phase III would be suitable for registration?

**FDA response:** See our response to Q13. With that in mind, we have no fixed idea about how many Black patients need to be enrolled; the number you have proposed is probably too small to yield a useful estimate of effect in that population.

**Discussion during meeting:** No further discussion.

- 23 Does the Agency agree that for vericiguat, a pediatric study waiver is justified for all age groups for the heart failure indication under Pediatric Research Equity Act (PREA)?

**FDA response:** The Division would support such a waiver, but this would require the submission of a waiver request that would be considered by the agency's Pediatric Review Committee.

**Discussion during meeting:** No further discussion.

- 24 The sponsors believe the results provided from the Phase IIb study are compelling and support the "Breakthrough Designation" criteria for preliminary clinical evidence and an unmet medical need for a serious condition. Does the Agency agree that based on the indication proposed and data provided, vericiguat meets the criteria to designate the program as breakthrough therapy?

**FDA response:** No. Based on the information we have at hand, the results of SOCRATES-reduced does not justify Breakthrough Designation.

**Discussion during meeting:** No further discussion.

#### **Additional Requests from the Agency**

1. Please submit all informed consent document(s). Please describe any country- or region-specific variations.
2. Please provide sample clinical trial kits, from both arms, identical to those used during VICTORIA. Ship them to Alexis Childers desk address in the same packaging as will be used for shipping to investigative sites.
3. Please submit all of your data management plans for VICTORIA, including all manual and programmatic checks.
4. Please submit your site monitoring plan for VICTORIA. If there are changes to your site monitoring plans were not documented contemporaneously by formal signed amendments, please explain the process for amending.

5. Please include all charters for committees involved in conducting VICTORIA (e.g., DSMB, Steering Committee, etc.)
6. All newsletters and all other communications to investigational sites and national coordinators from the group(s) responsible for the conduct of your trials. Please bookmark the newsletters by date.
7. Please submit, to the IND as soon as possible, an encrypted SAS dataset (no later version than 9.3) of the randomization list including the randomization number, treatment arm, and stratification factors (if any) for your Phase 3 trial. Please include an unencrypted copy of a DEFINE.PDF file describing the randomization list variables and an unencrypted cover letter. For time variables please indicate the time zone. If the randomization times have not been standardized to one time zone, please generate and submit a standardized randomization time variable. If randomization was done a particular way (for example, by block or if subjects were stratified by some factor), those variables should also be in the dataset. Password protection or zipped files are unacceptable. Send the encryption key separately via email to [esub@fda.hhs.gov](mailto:esub@fda.hhs.gov) ONLY (not anyone else in the Agency), put attention to Marina. A copy of the encryption key should also be included with your NDA submission of the trial results.

**Discussion during meeting:** No further discussion.

### **3.0 ADDITIONAL IMPORTANT INFORMATION**

#### **PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/U>

[CM360507.pdf](#). In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to:  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

### **DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

### **LABORATORY TEST UNITS FOR CLINICAL TRIALS**

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>).

### **ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for*

*Industry Assessment of Abuse Potential of Drugs*, available at:  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

### **Office of Scientific Investigations (OSI) Requests**

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

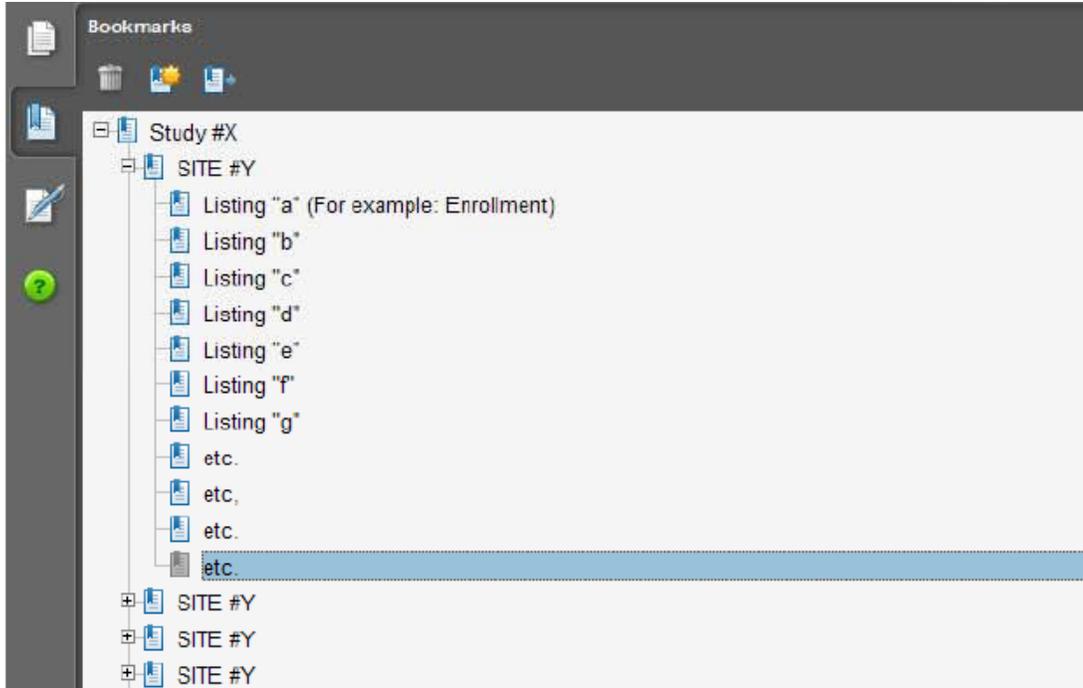
#### **I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
  - a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
  - a. Number of subjects screened at each site
  - b. Number of subjects randomized at each site
  - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:

- a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
  - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
  - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
  5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

## **II. Request for Subject Level Data Listings by Site**

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
  - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
  - b. Subject listing for treatment assignment (randomization)
  - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
  - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



### III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

**Attachment 1**  
**Technical Instructions:**  
**Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

<b>DSI Pre-NDA Request Item<sup>1</sup></b>	<b>STF File Tag</b>	<b>Used For</b>	<b>Allowable File Formats</b>
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

<sup>1</sup> Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1  
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page  
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

#### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

Proposed statistical analysis of the primary endpoint.

#### **5.0 ACTION ITEMS**

<b>Action Item/Description</b>	<b>Owner</b>	<b>Due Date</b>
Internally discuss proposed statistical analysis plan	FDA	TBD

#### **6.0 ATTACHMENTS AND HANDOUTS**

Sponsor presentation entitled “Vericiguat: End of Phase 2 Meeting, November 18<sup>th</sup>, 2015”

14 Page(s) 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 and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

ELLIS F UNGER  
12/11/2015