CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215341Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 117847

MEETING MINUTES

Bayer HealthCare Pharmaceuticals, Inc.
Attention: Dan Kim, Pharm.D., MBA
Associate Director, Global Regulatory Affairs
100 Bayer Boulevard
P.O. Box 915
Whippany, NJ 07981-0915

Dear Dr. Kim:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for finerenone (BAY 94-8862).

We also refer to the teleconference between representatives of your firm and the FDA on September 8, 2020. The purpose of the meeting was to discuss the top-line results of the FIDELIO-DKD trial and your planned NDA submission.

A copy of the official minutes of the teleconference 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 Anna Park, Regulatory Project Manager at (301)796-1129.

Sincerely,

{See appended electronic signature page}

Ellis Unger, M.D.
Director
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: September 8, 2020 from 12:00 PM – 1:00 PM
Meeting Location: Teleconference

Application Number: 117847
Product Name: Finerenone
Indication: To [redacted] reduce the risk of [redacted] cardiovascular [redacted] death, non-fatal myocardial infarction, [redacted] and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) and type 2 diabetes (T2D)
Sponsor Name: Bayer HealthCare Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(1)

Meeting Chair: Ellis Unger
Meeting Recorder: Anna Park

FDA ATTENDEES

Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)

Ellis Unger	Director
Ilan Irony	Acting Deputy Director

Division of Cardiology and Nephrology (DCN)

Norman Stockbridge	Director
Aliza Thompson	Deputy Director
Kimberly Smith	Medical Team Leader
Shen Xiao	Medical Officer
Mary Ross Southworth	Deputy Director for Safety
Michael Monteleone	Associate Director for Labeling

Division of Pharmacology/Toxicology for Cardiology, Hematology, Endocrinology, and Nephrology (DPT-CHEN)

Xuan Chi	Pharmacology Team Leader
Philip Gatti	Pharmacology Reviewer

Division of Regulatory Ops for Cardiology, Hematology, Endocrinology, and Nephrology (DRO-CHEN)

Edward Fromm	Chief, Project Management Staff
Anna Park	Regulatory Project Manager

Office of Clinical Pharmacology

Li Wang	Reviewer

Office of Biostatistics

Jialu Zhang	Team Leader
Steve Bai	Reviewer

SPONSOR ATTENDEES

Amer Joseph	Global Clinical Lead
Lothar Roessig	Global Clinical Development
Meike Brinker	Global Clinical Development
Andrea Horvat-Broecker	Global Safety Lead
Patrick Schloemer	Lead Statistician
Ingo Tornus	Global Program Head
Roland Heinig	Clinical Pharmacologist
Thomas Eissing	Pharmacometrics Strategist
Patty Hegarty	US Statistical Programming
Amit Sharma	Vice President, US Medical Affairs
Jay Elliott	US Medical Affairs
Ikenna Ogbaa	US Medical Affairs
Regina Seidel	Head of Cardiology and Nephrology, Global Regulatory Affairs
Susanne Metzger	Global Regulatory Strategist
Todd Paporello	Vice President and Head of Regulatory Affairs Americas
Sumana Biswas	US Regulatory Affairs
Dan Kim	US Regulatory Affairs

1.0 BACKGROUND

Finerenone (BAY 94-8862) is a non-steroidal, selective mineralocorticoid receptor antagonist (MRA) being developed for the treatment of patients with chronic kidney disease (CKD) and type 2 diabetes (T2D).

Bayer has completed the FIDELIO-DKD trial, a multicenter, randomized, double-blind, placebo-controlled, parallel-group study investigating the efficacy and safety of finerenone compared to placebo, on top of standard of care, on kidney disease progression and cardiovascular (CV) risk in 5,734 randomized subjects. The primary

endpoint was a composite of time to onset of kidney failure (ESRD or a sustained eGFR <15 mL/min/1.73m^2), a sustained decrease of eGFR ≥ 40% from baseline over at least 4 weeks, or renal death. The key secondary endpoint was a composite of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure. Other secondary endpoints included time to all-cause mortality, time to all-cause hospitalization, change in UACR from baseline to 4 months, and the composite endpoint of time to onset of kidney failure, sustained decrease in eGFR ≥57% from baseline over at least 4 weeks or renal death.

The purpose of this meeting is to present the results of the FIDELIO-DKD study and obtain agreement on Bayer's plan to submit a New Drug Application (NDA) in November 2020.

Preliminary responses to the submitted questions were provided to the Sponsor, and are copied below, followed by any additional discussions that took place during the meeting. The Sponsor used the appended slide presentation to guide the discussion at the meeting.

2.0 DISCUSSION

2.1. Clinical

Question 1:
Bayer intends to submit a New Drug Application (NDA) for finerenone for the following indication: "To (b) (4) reduce the risk of (b) (4) (b) (4) cardiovascular (b) (4) death, non-fatal myocardial infarction, (b) (4) and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) and type 2 diabetes (T2D)."
Does the Agency agree that the efficacy and safety data provided from the FIDELIO-DKD Phase 3 study are sufficient to support such an NDA submission?

Preliminary FDA Response:
We agree the data appear to be sufficient to support an NDA submission.

2.2. Regulatory

Question 2:
Does the Agency agree that the results provided from the FIDELIO-DKD study meet the criteria for Priority Review designation for the NDA?

Preliminary FDA Response:
Whether the NDA meets criteria for priority review designation will be determined after NDA submission; however, based on the information provided in the meeting materials, we believe the NDA is likely to qualify for the designation.

Question 3:
Does the Agency anticipate that an Advisory Committee meeting would take place for this NDA?

Preliminary FDA Response:
The need for an Advisory Committee meeting will be determined after NDA submission; however, based on the provided information, we do not anticipate that an Advisory Committee meeting will be needed.

Question 4:
Does the Agency agree with the Sponsor's plan to submit the NDA and that no barriers to filing have been identified?

Preliminary FDA Response:
Whether the NDA is fileable will be determined after NDA submission; however, we have not identified any barriers to filing based on the information provided in the meeting materials.

Discussion during the meeting:

Bayer provided an overview of the design of the FIDELIO-DKD Study (slide 5), a summary of baseline characteristics and disposition (slides 6), and then moved to the study's key efficacy findings. The trial met its primary endpoint with directional consistency amongst the components, although there were few renal deaths (slides 9 - 10). The trial also met its key secondary cardiovascular composite endpoint, with the findings driven by effects on cardiovascular death, nonfatal myocardial infarction, and hospitalization due to heart failure (slides 11-13). The incidence of non-fatal stroke was similar in both treatment arms. The primary and secondary endpoint findings were generally consistent across key subgroups (slide 14). The Sponsor also reported an ~30% reduction in urine albumin-to-creatinine ratio from baseline to Month 4 in the finerenone arm compared with placebo (slide 15).

Bayer noted a similar overall incidence of treatment-emergent adverse events in both treatment groups (slide 17). Adverse events of hyperkalemia or "blood potassium increased" were more common in the finerenone group than on placebo, as were elevated potassium levels on central laboratory assessment (slide 18). Bayer noted that mean serum potassium increased ~0.2 mmol/L from baseline to Month 4 in the finerenone group (slide 19). Bayer reported that hypotension and hyponatremia AEs were observed more frequently in the finerenone group, but most events were mild, non-serious, and rarely led to treatment discontinuation (slide 20).

The Division thanked the Sponsor for their presentation and congratulated the Sponsor on what appeared to be a well-conducted and successful trial.

The Sponsor asked whether the Division had preliminary feedback regarding the proposed indication:

> *"To* [redacted] *reduce the risk of* [redacted] *cardiovascular* [redacted] *death, non-fatal myocardial infarction,* [redacted] *and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) and type 2 diabetes (T2D)."*

The Division noted that the wording of the indication would be a review issue but that the indication was unlikely to include components of the composite that did not contribute to the treatment effect [redacted].

Post-meeting Comments:

Please provide the following information for the FIDELIO-DKD trial with your NDA submission:

a. Protocol and Statistical Analysis Plan (SAP)
   1. All versions of the trial protocols and SAPs and the dates when changes were implemented. For the trial protocols and SAPs, include a "Summary of Changes" for each version and information on the number of subjects enrolled and the number of primary endpoint events accrued at the time the change was made.

b. Clinical Trial Materials
   1. Sample clinical trial kits, from all treatment arms, identical to those used during the trials. Ship them to Anna Park's desk address in the same packaging as was used for shipping to investigative sites. Please email Ms. Park to alert her when she should expect this shipment.
   2. A description of the responsibilities of each academic research organization (ARO) or clinical research organization (CRO) used in the trials.
   3. All charters for committees involved in conducting your trials (Data Safety Monitoring Board [DSMB], Steering Committee, etc.).
   4. 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.

c. General Data and Analyses
   1. All script and datasets used to create your analyses found in the main sections of the Integrated Summary of Efficacy (ISE), Integrated Summary of Safety (ISS), and your phase 3 trial clinical study reports including code that was used to

create or clean up your analysis datasets. If the script contains macro, include the macro script. Footnote tables and figures with the name of the script used to create it.

2. Kaplan-Meier time to event analysis datasets and script (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.
3. 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.
4. Dataset that contains a list of all subjects for whom you submitted a case report form (CRF), or narrative. The dataset should contain three variables with an indicator for whether each item was submitted.
5. A table set up similarly to the dataset requested above but with a hyperlink to the respective document. The table could be further organized by reason for narrative submission.
6. One table which includes the following information for the trial:
   • Dates of first patient and last patient visits
   • Date of data lock
   • Dates of 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).

d. 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, 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.

e. 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), please reference the waiver and include the date.

2. Rationale for assuming the applicability of foreign data to the U.S. population and U.S. practice of medicine for any pivotal trials conducted primarily outside of the U.S.
3. An annotated version of the pre-NDA meeting minutes that include a hyperlink, when applicable, to the analysis and/or documents requested. This document is usually placed in Module 1.

3.0 OTHER IMPORTANT MEETING LANGUAGE

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our July 15, 2020 communication granting this meeting, 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.[1]

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

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*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

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[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- 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

[2] 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.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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.

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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[6]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[7]

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

[6] http://www.fda.gov/ectd
[7] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[8] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[9]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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,* and the associated conformance guide, *Bioresearch Monitoring Technical*

[8] https://www.fda.gov/media/84223/download
[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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*.[10]

4.0 ATTACHMENTS AND HANDOUTS

Please see the attached presentation titled “FDA Pre-NDA (Type B) Meeting, Finerenone (IND 117847)” dated September 8, 2020.

24 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

[10] 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/

ELLIS F UNGER
10/07/2020 02:43:46 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 117847

MEETING MINUTES

Bayer HealthCare Pharmaceuticals
Attention: Manini Patel
Deputy Director – Global Regulatory Affairs
100 Bayer Boulevard
P.O. Box 0915
Whippany, NJ 07981

Dear Ms. Patel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Finerenone (BAY 94-8862).

We also refer to the meeting between representatives of your firm and the FDA on April 27, 2015. The purpose of the meeting was to obtain the Agency's feedback on the adequacy of the Phase 2b (ARTS-DN) study and the proposed Phase 3 (b) (4) clinical development program.

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 Anna Park, Regulatory Project Manager at (301) 796-1129.

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:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: April 27, 2015, 2:30 PM – 4:00 PM, EST
Meeting Location: White Oak Bldg. 22, Room 1311

Application Number: 117847
Product Name: Finerenone (BAY 94-8862)
Indication: (b) (4)

Sponsor/Applicant Name: Bayer HealthCare Pharmaceuticals

Meeting Chair: Norman Stockbridge, M.D., Ph.D.
Meeting Recorder: Anna Park, R.Ph., RAC

FDA ATTENDEES

Ellis Unger, M.D.	Director, Office of Drug Evaluation I

Division of Cardiovascular and Renal Products

Norman Stockbridge, M.D., Ph.D.	Director
Aliza Thompson, M.D.	Medical Team Leader
Shen Xiao, M.D.	Medical Officer
Thomas Papoian, Ph.D.	Pharmacology Team Leader
Philip Gatti, Ph.D.	Pharmacology Reviewer
Anna Park, R.Ph.,RAC	Regulatory Project Manager

Office of Clinical Pharmacology

Rajnikanth Madabushi, Ph.D.	Clinical Pharmacology and Biopharmaceutics Team Leader

Office of Biostatistics

James Hung, Ph.D.	Director, Division of Biometrics I, Office of Biostatistics (OB)
John Lawrence, Ph.D.	Statistician

Office of Product Quality/ONDP

Mohan Sapru, Ph.D.	Acting CMC Lead (via phone)

SPONSOR ATTENDEES

Ingo Tornus, Ph.D.	Global Project Management
Nancy Cook-Bruns, M.D.	Head of Cardiovascular Group, Global Clinical Development
Christina Nowak, M.D.	Global Clinical Leader, Global Clinical Development
So-Young Kim, M.D.	Global Clinical Leader, Global Clinical Development
Roland Heinig, Ph.D.	Clinical Pharmacology Leader, Clinical Sciences
Peter Kolkhof, Ph.D.	Global Therapeutic Research
John Curram, Ph.D.	Project Statistician
Sabine Dittmar, M.D.	Global Pharmacovigilance
Carol Satler, M.D.	Global Medical Affairs
Yamin Wang, Ph.D.	Head of Regulatory Affairs, General Medicine
Todd Paporello, Pharm.D, MBA	Head of US Regulatory Affairs, Consumer Care
Santiago Figueroa Perez, Ph.D.	Global Regulatory Strategist
Manini Patel	Global Regulatory Strategist

1.0 BACKGROUND

Finerenone (BAY 94-8862) is a potent non-steroidal, selective mineralocorticoid receptor antagonist (MRA) being developed for the treatment of patients (b) (4) .

The Phase 2a dose-finding (minerAlocorticoid-Receptor antagonist Tolerability Study) ARTS study 14563 in patients with CHF and chronic kidney disease (CKD) demonstrated that finerenone doses of 2.5 to 10 mg/day reduced albuminuria in patients with CHF and CKD. There was a lower incidence of hyperkalemia and of renal side effects compared to spironolactone when finerenone was added to evidence-based therapy for HF that included a single RAS blocker, thus supporting finerenone's potential to treat (b) (4).

Two Phase 2b studies have been conducted to support (b) (4). The Phase 2b dose-finding ARTS-DN (ARTS-Diabetic Nephropathy) study 16243 showed that finerenone induced a dose-dependent (statistically significant for the 4 highest doses) reduction in urinary albumin-to-creatinine ratio (UACR) in patients with type 2 diabetes mellitus (T2DM) and DKD in combination with standard of care (SoC) therapy that included a single RAS blocker. Few cases of elevated serum potassium were reported. All investigated doses of finerenone showed a similar safety profile to that of placebo.

The Phase 3 clinical program aims to demonstrate the ability of finerenone to reduce the risk of CV events and to reduce progressive loss of renal function in patients with DKD. Two separate global, event-driven Phase 3 trials are planned to confirm the efficacy and safety of finerenone in 2 distinct subgroups of patients with T2DM and DKD.

An End-of-Phase 2 meeting was held on April 27, 2015 to obtain feedback on the adequacy of the Phase 2b (ARTS-DN) study and the proposed Phase 3 (b) (4) clinical

development program. Preliminary responses to the submitted questions were provided to the sponsor in advance of the meeting. Bayer provided written responses to the Division's preliminary responses to Questions 6, 9, 11, 12, 14, 20, and 22. These written responses, along with a slide presentation, were used to guide the discussion during the meeting.

2. DISCUSSION

2.1. CMC

Question 1(10.2.1 CMC.1): *Does the Agency agree to Bayer's proposal using the following* (b) (4) (b) (4) *as starting materials in the synthesis of BAY 94-8862 for the marketing application submission?*

Preliminary FDA Response: Your strategy (b) (4) (b) (4) based on a risk assessment approach and in compliance with guidance from ICH Q11 and ICH M7 is acceptable.

Additional discussion during the meeting: None.

2.2. Nonclinical

Question 2 (10.3.1 NC.1): *Does the Agency agree that the completed, ongoing, and planned nonclinical safety studies for finerenone are adequate to support the planned Phase 3 studies and the marketing applications for the proposed* (b) (4) *indication?*

Preliminary FDA Response: Yes, we agree.

Additional discussion during the meeting: None.

Question 3(10.3.2 NC.2): *Does the Agency agree that the major human metabolites of finerenone are adequately characterized by the completed, ongoing and planned nonclinical safety studies with finerenone to support the planned Phase 3 studies and the marketing application for the proposed* (b) (4) *indications?*

Prelimninary FDA Response: Yes, we agree. There are no pharmacologically active metabolites or any unique human metabolites of BAY 94-8862. Plasma levels of the major human metabolites (M-1, M-2, M-3) that were measured in 13-week repeat-dose toxicity studies in mouse, rat and dog were adequate (levels measured were at least equal to levels measured in plasma of subjects in the clinical studies) to allow an adequate assessment of these metabolites.

Additional discussion during the meeting: None.

2.3. Clinical Development - Clinical Pharmacology

Question 4 (10.4.1.1 CP.1): *Does the Agency agree that the completed, planned and ongoing clinical pharmacology studies and the data generated to date to characterize the pharmacokinetic/pharmacodynamic (PK/PD) profile of finerenone are sufficient to support initiation of the Phase 3 studies in subjects with DKD?*

Preliminary FDA Response: Yes.

Additional discussion during the meeting: The Agency asked what might explain the increase in exposure in subjects with renal impairment, as this was not expected *a priori*. The sponsor stated that they were also surprised by the finding and attributed it to impaired hepatic function in patients with renal impairment.

Question 5 (10.4.1.2 CP.2): *Does the Agency agree that the effect of hepatic insufficiency on the PK of finerenone is adequately characterized based on the hepatic impairment study (14510) results?*

Preliminary FDA Response: Yes.

Additional discussion during the meeting: None.

Question 6 (10.4.1.3 CP.3): *Does the Agency agree with the proposed population pharmacokinetics sparse sample collection plan in the proposed Phase 3 studies for DKD?*

Preliminary FDA Response: You propose sparse sample collection to investigate the covariate/exposure relationship. There is no reason to expect that previously unidentified covariates that significantly impact exposure will be identified in a subset of 500 patients in Phase 3. Instead, we recommend that you obtain PK information from phase 3 studies that will allow characterization of exposure-response with respect to efficacy and safety. Consider obtaining PK samples from all subjects in Phase 3. We look forward to a discussion with you on how to decide post-hoc which samples to analyze.

Bayer's Response: *Bayer acknowledges the Division's comment and has carefully considered the Division's recommendation for obtaining PK samples from all subjects in Phase 3. Bayer still considers that the planned PopPK analysis in a PK subpopulation of 500 patients will be sufficient for the following reasons:*

- *The PopPK/PD models were built to describe the exposure/response relationship for the safety and efficacy markers, serum potassium, eGFR, and UACR. The PK/PD models were turnover models describing delayed effects of finerenone on these markers in which a pharmacokinetic steady-state for finerenone was reached on the second day of dosing, while a steady-state for the PD markers was reached much later (95% of steady-state reached after 10 days (serum potassium), 43 days (eGFR) and 89 days (UACR), respectively). Bayer has looked at the exposure in patients with clinically relevant adverse event (i.e., hyperkalemia,) and there was no obvious relationship between*

finerenone exposure and the occurrence of this adverse event across all tested finerenone doses.

- *Sparse sampling and population-pharmacokinetic/ dynamic (popPK/PD) analyses were conducted in all patients in the Phase 2a (study #14563) and Phase 2b (study #16243) trials. Based on these analyses the PopPK model for finerenone was developed and refined, describing the PK of finerenone as dose- and time-linear with estimated glomerular filtration rate (eGFR) and body-weight identified as covariates for apparent oral clearance and volume of distribution, respectively. Predictions of quantitative changes in exposure based on these covariates were derived from the model. The effect of impaired renal function on exposure estimated by the popPK model is consistent with the findings of a dedicated Phase 1 study in subjects with varying degrees of renal impairment. After correction for the identified relevant covariates the estimated apparent oral clearance of finerenone was comparable in healthy volunteers and patients in the Phase 2 studies (i.e., disease itself had no influence on exposure). The identified covariates and the size of their effects on finerenone exposure were also consistent across the Phase 2 studies.*
- *Thus, the objective of the planned PopPK analysis in a PK subpopulation of 500 patients receiving finerenone in Phase 3 studies is to collect more exposure data, specifically in populations for which no or very few data have become available in previous studies (i.e., African-American and Hispanic patients) and determine finerenone exposure in comparison to a population of Caucasian patients. This analysis is planned in selected study centers in which patient recruitment will be focused on the above populations. Bayer considers that the planned PK-subpopulation in Phase 3 is sufficient to complement the already available information on the covariate/exposure relationship and support the comparison of exposure in Phase 2 and Phase 3 studies.*

  Bayer appreciates the opportunity to discuss this further during the meeting with the Division.

Additional discussion during the meeting: The Division noted that finerenone PK-outcome relationships have not been characterized and reiterated its recommendation to collect PK samples in all subjects. The Division stated that these data would provide valuable insight into the relationship between exposure and important clinical outcomes and could potentially be used to inform dosing recommendations in labeling. Bayer stated that they would take the Division's advice under consideration and follow up with the Division on the specifics of their sampling approach.

2.4. Clinical

Question 7 (10.4.2.1 CD.1): *Does the Agency agree that the two planned Phase 3 studies support each other, and that the two studies support the registration for the proposed* (b) (4) *indication?*

Preliminary FDA Response: Yes.

Additional discussion during the meeting: None.

Question 8 (10.4.2.2 CD.2):

a) Does the Agency agree with the proposed study populations of the two Phase 3 DKD studies to support the proposed indication?

Preliminary FDA Response: Yes.

Additional discussion during the meeting: None.

b) Does the Agency agree with the inclusion and exclusion criteria?

Preliminary FDA Response: Yes.

Additional discussion during the meeting: Dr. Thompson encouraged the sponsor to consider studying patients with more severe renal impairment in their development program, especially if early data from their phase 3 trial provide reassurance of safety. She also indicated that it might be possible to include this population in the phase 3 trial but prespecify their exclusion from the primary efficacy endpoint analysis, but that this would require further discussion.

Question 9 (10.4.2.3 CD.3):

a) Does the Agency agree with the following proposed efficacy outcome measures for the RENAL-DKD study 16244?

- *Primary efficacy outcome:*
  - *Time to first occurrence of renal composite: onset of kidney failure, or sustained GFR decrease ≥40% from baseline over at least 4 weeks or renal death*
- *Secondary efficacy outcome:*
  - *Time to first occurrence of CV composite: CV death, or non fatal CV events (non-fatal MI, non-fatal stroke, unplanned hospitalization for HF or equivalent*
  - *Time to all-cause mortality*
  - *Time to all-cause hospitalizations*

Preliminary FDA Response: Yes, however we question whether your definition of renal death is appropriate. According to your briefing document, renal death will be defined as a death occurring after the patient refuses renal replacement therapy (i.e., initiation of chronic dialysis or renal transplantation) or after the physician, with or without patient consent, withholds a regular course of chronic dialysis. Although there is no standardized definition of "renal death," the definition often excludes deaths due to another primary process and/or when another cause is adjudicated (sepsis, end-stage heart failure, advanced malignancy, etc.). Also, it is unclear from your submission whether you plan to adjudicate renal deaths in your phase 3 trials. Patients with renal failure often develop multi-organ failure, infections, etc. Thus, rules for adjudication of deaths must be explicit, and because some judgment will be involved in decision making, we recommend that you establish an adjudication panel.

Bayer's Response: *Bayer appreciates the feedback given by the Division with regards to renal death and adjudication.*

Bayer's definition of renal death is derived from previously conducted phase 3 trials in DKD/CKD studies (ie BEACON, ALTITUDE). Bayer does agree that patients with renal failure often suffer multi-organ failure and infection. The CEC charter will include explicit rules for adjudication of deaths. One Clinical Event Committee (CEC) will be established for the phase 3 program of finerenone to adjudicate all study endpoints, including all deaths and amongst them renal deaths. Considering the feedback given by the Division, deaths which will have renal failure as leading cause will also be adjudicated as "renal death". However, this can only be decided on a case by case basis as multi-organ failure or infection can also derive from other underlying diseases. Bayer appreciates the opportunity to discuss this topic with the Division.

Additional discussion during the meeting: The Division agreed with the sponsor's proposal to establish a blinded, independent adjudication committee and to specify explicit rules for adjudication of deaths in the CEC charter.

b) Would the Agency agree to including the secondary efficacy outcome results in the labeling, assuming a positive result in the primary outcome measure and statistically significant results for the secondary outcomes?

Preliminary FDA Response: Yes, assuming the findings from CV-DKD study 17530 are also supportive. See also our response to Question 21*(10.4.3.8 St.8).*

Additional discussion during the meeting: None.

Question 10 (10.4.2.4 CD.4):

a) Does the Agency agree with the following proposed efficacy outcome measures for the CV-DKD study 17530?

- *Primary efficacy outcome:*
  - *Time to first occurrence of CV composite: CV death, or non-fatal CV events (non-fatal MI, non-fatal stroke, unplanned hospitalization for HF or equivalent)*
- *Secondary efficacy outcome:*
  - *Time to first occurrence of renal composite: onset of kidney failure, or sustained eGFR decrease ≥40% from baseline over at least 4 weeks, or renal death*
  - *Time to all-cause hospitalizations*
  - *Time to all-cause mortality.*

Preliminary FDA Response: Yes.

Additional discussion during the meeting: None.

b) Would the Agency agree to including the secondary outcome results in the labeling, assuming a positive result in the primary outcome measure and statistically significant results for the secondary outcomes?

Preliminary FDA Response: Yes, assuming the findings from RENAL-DKD study 16244 are also supportive.

Additional discussion during the meeting: None.

Question 11 (10.4.2.5 CD.5): *Does the Agency agree with other elements of study designs including background therapy, visit frequency and treatment duration for the two planned Phase 3 studies for DKD?*

Preliminary FDA Response: Yes, however you may want to consider adding a second run-in phase in which all subjects are treated with finerenone to enrich for subjects who are able to tolerate the drug. Such a strategy will reduce the numbers of subjects who discontinue therapy. Specifically, you should consider excluding subjects who develop clinically significant elevations in potassium or decrements in renal function during such a run-in phase. We also recommend limiting routine laboratory monitoring to what is needed to characterize the safety of your product. With two large studies proposed, we would like to discuss ways the burden of monitoring might be reduced.

Bayer's Response: *Bayer acknowledges Division's comments. Bayer's strategy to select the population that can better tolerate the drug was to choose conservative potassium cut off (less than 4.8 mmol/L) for eligibility). In addition, a 2-step up-titration of finerenone was chosen which is consistent with current clinical practice to initiate treatment with a RAS blocker at a low dose, and up-titrate the drug only if tolerated in order to avoid adverse effects on potassium and renal parameters. Based on our current phase 2 program in more than 1900 patients exposed to finerenone, Bayer believes that the second run-in phase is not required. Nevertheless, Bayer is interested in exploring the option of including a second run in phase during the meeting with the Division. In particular, Bayer would appreciate Division's feedback on the possible run-in duration, study drug dosing, stopping and discontinuation rules that would need to be considered for a second run-in phase. Additionally, Bayer is interested how the information on the second-in phase would be described in label.*

Bayer also acknowledges Division's recommendation for limiting routine laboratory monitoring to what is needed to characterize the safety for finerenone and would be interested in Division's feedback for potential ways of reducing the burden of monitoring.

Additional discussion during the meeting: Bayer discussed their rationale for not including a second run-in phase in the trial (see "Bayer's Response" above). The Division indicated that the decision to include a second run-in phase was up to the sponsor. If a second run-in phase were used, it would be important to capture the reasons for discontinuation of therapy during this phase. In response to the sponsor's question about how a second run-in phase would be described in labeling, the Division indicated that the design of the trial,

including the use of a run-in phase, would be described in Section 14 (Clinical Studies) and that information on safety and tolerability during the run-in phase might also be included in Section 6 (Adverse Reactions).

The discussion turned to other issues. The Division encouraged the sponsor to come up with a proposal for limiting routine laboratory monitoring to what was necessary to characterize the safety of their product. The Division also encouraged the sponsor to use Standardised MedDRA Queries (SMQs) to characterize finerenone's safety in any future NDA.

Question 12 (10.4.2.6 CD.6): *Does the Agency agree with the initiation of the two Phase 3 trials intended for registration with the proposed dose(s) of finerenone?*

Preliminary FDA Response: No. The results of study 16243 and the subsequent post hoc analysis do not warrant a lower starting dose in patients with eGFR < 60 mL/min/1.73 m^2. There is a clear trend for a dose-dependent decrease in UACR ratio. However, the same is not true for increases in serum potassium. The possibility of down-titrating the finerenone dose based on serum potassium would be reasonable.

Given the short half-life of finerenone, a BID regimen would be expected to provide relatively higher exposure throughout the inter-dosing interval compared to a once daily regimen. The results of study 13785 indicate a significant increase in plasma-renin activity and aldosterone levels with the BID regimen compared to the QD regimen. We would like to discuss your rationale for not exploring a BID regimen for this indication.

Bayer's Response: *Bayer acknowledges the Division's comments regarding dosing and would appreciate the opportunity to discuss dosing in conjunction with the topic on second–run-in phase.*

Based on all available finerenone data, dose dependent increase in serum potassium has been observed. This finding has been also confirmed in the exposure-response analysis. Bayer is of the opinion that initiating with a lower dose and titrating to a higher dose as tolerated is consistent with clinical practice. Hence, a 2-step up-titration of finerenone was selected to optimize the benefit-risk profile.

Bayer's rationale for using QD instead of BID are as follows:

- *Prior to undertaking the finerenone clinical development program, available MRA data suggested longer duration of action compared to pharmacokinetics of the drug.*[1]

- *While study 13785 appeared to indicate a more pronounced increase in plasma-renin activity and aldosterone levels with the BID regimen compared to the QD regimen, this observation was not confirmed in study 15171, a multiple-dose trial in healthy*

[1] A Comparison of the Aldosterone-blocking Agents Eplerenone and Spironolactone Allan Struthers, MD, Henry Krum, MD, PhD,∗ Gordon H. Williams, MD

Japanese subjects conducted using the same design as study 13785. In study 15171, the changes in plasma renin activity on day 10 compared to baseline were similar after administration of 10 mg BID, 20 mg BID and 40 mg QD. Mean aldosterone levels on day 10 of study 15171 (51.7 and 47.0 ng/L; 20 mg BID and 40 mg QD) were also similar between the BID and QD regimens.

- *The PK/PD models developed for finerenone on the basis of Phase 2 trials are turnover models which indicate an indirect relationship between drug exposure and response parameters. In spite of the short half-life of finerenone of 2-3 hours the effects on pharmacodynamic parameters are long-lasting with half-lives for the effects on UACR, serum potassium and GFR of about 18 days, 2 days and 9 days. This suggests that it is required for finerenone to reach systemic concentrations inhibiting the mineralocorticoid receptor but not to maintain these concentrations for an extended period of time. Unbound maximum plasma concentrations of finerenone above the IC50 of the target receptor were reached in patients of the Phase 2b study at relevant doses. This mode of action and exposure/response model do not suggest that a concentration vs. time profile resulting from BID dosing would be required.*

- *The ARTS was the first study to assess different finerenone doses and dosing regimens over 28 days of treatment in a patient population including once daily (QD) and twice daily dosing (BID). The most pronounced increase of serum potassium (and thus the risk of hyperkalemia), was observed in the finerenone 5 mg BID treatment group compared to the 5 mg and 10 mg QD treatment groups (according to the ANCOVA of the mean change from baseline to visit 6 (day 22±2) and 7 (day 29±2)). The effects on natriuretic peptides and albuminuria in patients with either micro- or macro-albuminuria were comparable between the 5 mg BID treatment group, the 5 mg QD treatment group, and the 10 mg QD treatment group. The effect on aldosterone levels was comparable between the 5mg BID treatment group and the 10mg QD treatment group. This finding suggests that the MR blocking effects of both doses are similar. As a result, once daily dosing was selected in the in Phase 2b studies 14564 (Phase 2b study in WCHF) and 16243 (Phase 2b study in DN).*

  Based on the above Bayer still considers QD dosing as appropriate for the phase 3 program.

<u>Additional discussion during the meeting:</u> Bayer discussed their rationale for using a QD instead of a BID dosing regimen (see discussion above and attached slides). Dr. Madabushi did not think there was compelling evidence that a BID regimen was associated with a higher serum potassium level than was a QD regimen.

The sponsor indicated that safety was an important consideration in dose selection. Dr. Madabushi stated that this approach, although reasonable, may not fully realize finerenone's efficacy potential. The sponsor acknowledged this risk but felt comfortable with the proposed approach to start with a lower dose (10 mg) and titrate to a higher dose as tolerated (20 mg), with down-titration as needed.

Question 13(10.4.2.6 CD.7): *Based on the available QTc results, does the Agency agree that performing local ECG reading is adequate in Phase 3 studies for DKD?*

Preliminary FDA Response: Yes.

Additional discussion during the meeting: None.

2.5. Statistical

Question 14 (10.4.3.1 St.1): *Does the Agency agree with the proposed statistical analysis of the primary efficacy endpoint?*

Preliminary FDA Response: Yes. However, a possible scenario is that one of the trials achieves a p-value < 0.05 on the secondary endpoint but the primary endpoint does not reach statistical significance, in which case this secondary endpoint should not be tested based on your proposed hierarchical testing strategy. Consequently, it is unclear if the result of the secondary endpoint in this trial can be used as supportive evidence. You may want to think about this carefully and we are open to further discussion in the meeting. There are alternative ways to construct the statistical testing paradigm, and these merit discussion.

Bayer's Response: *Bayer acknowledges and appreciates the Division's feedback and has carefully considered the Division's feedback. We can confirm that in the current company position included in the briefing document for a hierarchical testing procedure, if the primary endpoint does not achieve statistical significance at a two-sided p-value ≤ 0.05, then formally the top secondary endpoint cannot be tested. To be able to make this test if the primary endpoint fails to achieve statistical significance, Bayer has considered two alternative approaches and is open to discussing these as well as other approaches that the Division considers more appropriate for the testing procedure.*

One possible approach would be the fallback procedure1[2]. The primary endpoint is tested at a level α1, the remaining α2 is held back for the top secondary endpoint, such that α1 + α2 = 0.05. If the primary endpoint achieves statistical significance at a two-sided p-value ≤ α1, the top secondary endpoint can be tested at the 0.05 level; otherwise it can still be formally tested at a lower level of α2. Further secondary endpoints can be tested at the same level as the top secondary endpoint, should this achieve formal statistical significance.

Another possibility is a weighted Bonferroni-Holm procedure[3]. With one primary endpoint and one top secondary endpoint this simplifies to the following rule:

- *If the primary endpoint achieves statistical significance at a two-sided p-value ≤ α1, the top secondary endpoint can be tested at the 0.05 level.*
- *Alternatively if the top secondary endpoint achieves statistical significance at a two-sided p-value ≤ α2, the primary endpoint can be tested at the 0.05 level.*

[2] Brian L Wiens & Alexei Dmitrienko (2005). The Fallback Procedure for Evaluating a Single Family of Hypotheses, Journal of Biopharmaceutical Statistics, 15:6, 929-942.
[3] Frank Bretz, Willi Maurer and Jeff Maca, in Walter Young and Ding-Geng (Din) Chen (2014), Clinical Trial Biostatistics and Biopharmaceutical Applications, Chapman & Hall/ CRC. Chapter 14, page 412

• *Only if both the primary and top secondary endpoints achieve formal statistical significance, can further secondary endpoints be tested.*

Bayer also acknowledges that by using either of the above approaches, to preserve the power of the study for the pre-defined primary endpoint at 90% given α1, this will require more events to be observed before the study can be stopped, resulting in more subjects to be randomized or the study duration to be extended. If the alpha is equally divided between the primary and top secondary endpoints, then it is estimated that this would increase the required number of events by approximately 20%; if the alpha is divided two-thirds to the primary endpoint and one-third to the top secondary endpoint, then the increase is approximately 10%.

In addition, Bayer would like to get clarification for the Division's comment on the stated "p-value < 0.05" in the response to Question 14. Bayer has used a one-sided p-value of 0.025 in the company position.

Does the Agency have a preference for a two-sided or a one-sided test to be specified in the protocols?

Additional discussion during the meeting: The Division recommended the Bonferroni-Holm procedure with a two-sided test.

Question 15 (10.4.3.1. St.2): *Does the Agency agree with the proposed testing procedure for the secondary endpoints?*

Prelimimary FDA Response: Yes. Also see the response to Q14.

Additional discussion during the meeting: None.

Question 16 (10.4.3.3 St.3): *Does the Agency agree with the proposed analysis sets designated for the safety and efficacy analyses?*

Preliminary FDA Response: Yes.

Additional discussion during the meeting: None.

Question 17 (10.4.3.4 St.4): *Does the Agency agree with the predefined stratification and subgroup analysis strategy?*

Prelimnary FDA Response: Yes.

Additional discussion during the meeting: None.

Question 18(10.4.3.5 St.5): *Does the Agency agree with the methods proposed to minimize missing data, and the approaches for the handling of missing data?*

Preliminary FDA Response: Yes.

Additional discussion during the meeting: None.

Question 19(10.4.3.6 St.6): *Does the Agency agree with the proposed sample size calculation?*

Preliminary FDA Response: Yes.

Additional discussion during the meeting: None.

Question 20 (10.4.3.7 St.7): *Does the Agency agree with the proposed details of the planned interim analysis?*

Preliminary FDA Response: According to your briefing document, the Haybittle-Peto rule will be used to guide the decision regarding early stopping of the CV-DKD study for success. Specifically, a reduction of 3 standard deviations (of the test statistic) in the analysis of the primary efficacy endpoint at the interim analysis (one-sided p-value < 0.00135) will be required for early stopping for success. The Haybittle-Peto rule will be also used to guide the decision regarding early stopping of the study for success of the RENAL-DKD study, with the requirement that both the primary efficacy endpoint at the interim analysis and the secondary CV composite endpoint have a one-sided p-value < 0.00135. If the p-value for the primary endpoint in RENAL-DKD is not highly persuasive, however, the strategy may not provide the data needed to support an effectiveness claim related to the progression of renal disease.

We also recommend that you use the same DMC for both phase 3 trials.

Bayer's Response: *Bayer acknowledges the Division's comments regarding planned interim analysis and would like to clarify the rule for the RENAL-DKD study. To stop this study at the interim analysis, we require the renal composite endpoint to have a one-sided p < 0.00135 and the CV composite endpoint to have a one-sided p < 0.00135, which we would consider highly persuasive evidence for both endpoints. We would be pleased to discuss this with the Division if further clarity is required.*

Bayer also confirms that one DMC is planned for both phase 3 trials, comprising of independent external cardiologists, nephrologists and endocrinologists, and a statistician, all of whom are experienced and outstanding experts in their area of expertise. These individuals have previously served on other DMC.

Additional discussion during the meeting: The Division stated that the sponsor's proposal was acceptable. A one-sided p-value can be used to determine whether to stop the trial at an interim time but the final report should include two-sided p-values.

Question 21(10.4.3.8 St.8): *Does the Agency agree that an exploratory pre-planned integrated efficacy and safety analysis is acceptable as supportive evidence?*

Preliminary FDA Response: See our response to Q14.

Additional discussion during the meeting: None.

2.6. Clinical Safety

Question 22 (10.4.4.1 Saf.1): *Does the Agency agree with the management and stopping rules for hyperkalemia in the Phase 3 trials?*

Preliminary FDA Response: The approach described in the appendices of your Extended Study Concept documents for your phase 3 trials seems reasonable. Investigators should also be directed to perform an immediate ECG if the potassium level exceeds some threshold.

Bayer's Response: *Bayer acknowledges and appreciates the Division's comments. Bayer will ask investigators to perform an immediate ECG in patients with severe hyperkalemia (serum potassium ≥ 7.0mmol/L) or in symptomatic patients.*

Additional discussion during the meeting: The Division reiterated its recommendation to mandate urgent ECG testing based on serum potassium concentrations greater than a particular threshold value. Making the assumption that a high potassium value is secondary to hemolysis or laboratory error and waiting to act until a confrimatory test is obtained can have fatal consequences. The Division advised the sponsor to include written justification for the proposed potassium threshold in their protocol submission.

Question 23 (10.4.4.2 Saf.2): *With regard to reporting procedures for serious adverse events (SAEs) that are also potential study endpoints, does the Agency concur that these events should be treated as study endpoints only, and that the requirement for SAE reporting be waived?*

Preliminary FDA Response: Yes.

Additional discussion during the meeting: None.

2.7. Multidisciplinary – Regulatory Aspects

Question 24 (10.5.1 R.1): Pediatric Development
Does the Agency agree to the request for a waiver to conduct pediatric studies in DKD?

Preliminary FDA Response: We agree that your proposal to request a waiver seems reasonable. As noted in Section 3 below, you must submit your Initial Pediatric Study Plan within 60 days of your End of Phase 2 meeting.

Additional discussion during the meeting: None.

Question 25 (10.5.2 R.2): Target Product Profile
Based on the summary information provided in this Briefing Information Package, and assuming positive study results, does the Agency concur with the proposed target product profile (TPP)? The proposed TPP is detailed in Section 13.2 of this Briefing Document.

- ***Section 1: Indication and Usage***
  - *Does the FDA have any comments on the proposed indication statement including FDA's thoughts on the describing* (b) (4) (b) (4) *?*
  - *Does FDA have any other consideration related to appropriately communicating a meaningful indication to the prescribing physicians?*
  - *Does FDA see a limitation of use for promotional claims?*

- ***Section 2: Dosage and Administration***
  - *Does the Division agree with Bayer's proposed text* (b) (4) (b) (4)

- ***Section 14: Clinical Studies***
  - *Based on Bayer's reading of the FDA's "Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format," the description of study 16244 and 17530 in labeling should be quite detailed. We propose* (b) (4) (b) (4) (b) (4) *Agency agree?*

  - *Bayer is interested in presenting efficacy results in the Black and Hispanic population in Section 14 of the Prescribing Information. To achieve this, what would Bayer need to consider?*

  - *To what extent would secondary outcomes be presented in labeling should the one-sided p-value of <0.025 (assuming consistency across subgroups and an acceptable overall risk/benefit profile)?*

    Preliminary FDA Response: For the most part, your proposed Target Product Profile seems reasonable. We have the following comments at this time:
    - Proposed Indication. Your proposed indication is for the for the treatment of (b) (4) adult patients with type 2 diabetes mellitus to reduce:

- the risk of CV mortality [redacted]., non-fatal myocardial infarction, [redacted] or hospitalization for heart failure [redacted]
- [redacted]

The exact wording of your indication statement will be a review issue; however, if you establish a CV benefit, we will likely refer to your therapy as a treatment for adult patients with type 2 diabetes mellitus [redacted]

- Section 14 Clinical Studies.
  1. We agree that Section 14 should show the results for all components of your key composite endpoints. As noted in FDA's Guidance Document titled "Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format," unless a component has been assessed as a separate endpoint with a prospectively defined hypothesis and analysis plan that controls Type-I error, discussion of a component should be only descriptive. For example, a table showing effects on a composite endpoint would show the breakdown by first event but would not include a p-value.
  2. We are also interested in seeing efficacy results presented for the Black and Hispanic population and encourage you to enroll these patients in your trials.

The proposed text for [redacted] renal and hepatic impairment seems reasonable.

Additional discussion during the meeting: None.

Question 26 (10.5.3 R.3): Breakthrough Designation
Bayer is interested in pursuing breakthrough therapy designation for finerenone [redacted]. Would the results from the Phase 2b ARTS- DN study be sufficient to obtain breakthrough therapy designation?

Preliminary FDA Response: We agree that [redacted] is a serious disease; however, on its face, we do not believe that the preliminary clinical evidence described in your submission would be sufficient to grant Breakthrough Therapy designation.

[redacted]

In sum, we (b) (4) do not believe the cited data are sufficient to indicate that your drug may demonstrate substantial improvement in effectiveness.

Additional discussion during the meeting: None.

3.0 OTHER IMPORTANT LANGUAGE

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email 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

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/default.htm).

4.0 ATTACHMENTS AND HANDOUTS

Attached below.

4 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANNA J PARK
05/27/2015

NORMAN L STOCKBRIDGE
05/27/2015