

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211617Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106654
IND 130707

MEETING PRELIMINARY COMMENTS

Esperion Therapeutics, Inc.
Attention: Ashley Hall, JD
Vice President, Global Regulatory Affairs
3891 Ranchero Drive, Suite 150
Ann Arbor, MI 48108

Dear Ms. Hall:

Please refer to your Investigational New Drug Applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for bempedoic acid (IND 106654) and bempedoic acid/ezetimibe fixed dose combination (FDC)(IND 130707, respectively.

We also refer to your May 25, 2018, correspondence requesting a meeting to discuss your to-be-submitted NDAs.

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, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comment



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: September 6, 2018, 12:30 – 1:30 pm
Meeting Location: FDA White Oak, Bldg 22, Conference Room 1309

Application Number/Product Name: IND 106654-Bempedoic acid
IND 130707-Bempedoic acid/ezetimibe FDC

Indications: Adjunct to diet and maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or atherosclerotic cardiovascular disease (ASCVD) who require additional LDL-C lowering.

Sponsor/Applicant Name: Esperion Therapeutics

FDA ATTENDEES (tentative)

Office of Drug Evaluation II

Mary Thanh Hai, MD-Director (Acting)

Division of Metabolism and Endocrinology Products

William Chong, MD-Director (Acting)

John Sharretts, MD-Clinical Team Leader (Acting)

Iffat Chowdhury, MD-Clinical Reviewer

Calvin (Lee) Elmore, PhD-Supervisory Toxicologist

Lydia Haile, PhD-Nonclinical Reviewer

Kati Johnson-Senior Regulatory Project Manager

Office of Biometrics II, Division of Biometrics II

Anna Kettermann, PhD-Statistical Reviewer

Office of Clinical Pharmacology (OCP), Div. of Clinical Pharmacology II (DCPII)

Jaya Vaidyanathan, PhD-Clinical Pharmacology Team Leader

Shalini Wickramaratne Senarath Yapa, PhD-Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

Ashley Hall, JD, RAC-Senior Vice President, Global Regulatory Affairs and Policy

Bill Sasiela, PhD-Senior Vice President, Clinical Development

Carla Griffin, MA-Senior Manager, Global Regulatory Affairs

Clay Cramer, MS-Director, Non-Clinical Development

Diane MacDougall- Senior Director, Clinical Development
LeAnne Bloedon, MS, RD-Senior Director, Clinical Development
Narendra Lalwani, PhD-Executive Vice President of Research & Development and COO
Sandeep Kumar, PhD-Senior Director, Regulatory Affairs
Maury Emery, PhD-Director of Clinical Pharmacology

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 6, 2018, FDA White Oak, Bldg. 22, Conference Room 1309 between Esperion and the Division of Metabolism and Endocrinology 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

IND 106654 was submitted September 23, 2009, for the [REDACTED] (b) (4). Initial agency reviews described the compound as a dual PPAR (α , γ) agonist, but further pharmacology studies exploring the mechanism of action indicated bempedoic acid to be an adenosine triphosphate-citrate lyase (ACL) inhibitor.

As with all peroxisome proliferator activated receptor (PPAR) agonists (submitted since around 2004), the IND was put on Partial Clinical Hold on November 19, 2009, for clinical studies in excess of 6 months until draft reports from completed 2-year rat and mouse carcinogenicity studies were submitted. Special Protocol Assessment requests were submitted for the proposed rat (SPA-1) and mouse carcinogenicity (SPA-2) studies on February 10, 2012, and March 20, 2012, respectively; agreement letters issued March 29, 2012, and May 3, 2012, respectively. Following submission of completed carcinogenicity study reports, the Partial Clinical Hold was removed January 29, 2015.

On December 12, 2012, the application was again placed on Partial Clinical Hold for daily doses in excess of 240 mg based on results from preclinical studies. This Partial Clinical Hold was removed on July 1, 2015.

In response to a May 7, 2015, meeting request, an end-of-phase 2 (EOP2) meeting was held on August 11, 2015, to discuss the firm's proposed development plan for the following proposed indications:

ETC-1002 is indicated as an adjunctive

(b) (4)

(b) (4)

On August 10, 2015, in response to the Division's preliminary comments, the firm submitted a "revised clinical study plan," which included a revised proposed indication: "ETC 1002 is indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) requiring additional lowering of LDL C." Meeting minutes issued on September 10, 2015.

Following the EOP2 meeting, on November 9, 2015, Esperion requested

(b) (4)

(b) (4)

(b) (4)

On January 26, 2016, the firm submitted protocol 1002-043, titled, *A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Effects of Bempedoic Acid (ETC 1002) on the Occurrence of Major Cardiovascular Events in Patients with, or at high risk for, Cardiovascular Disease who are Statin Intolerant* for review under the Special Protocol Assessment (SPA-3) process. A "No Agreement" letter issued on March 11, 2016. The firm resubmitted a revised protocol on April 21, 2016, and a "No Agreement" letter issued June 8, 2016.

On February 18, 2016, the firm requested a meeting to obtain the Agency's advice and agreement on the newly proposed Phase 3 clinical development program and discussion of a

(b) (4)

In a submission dated March 9, 2017, the firm requested

(b) (4)

(b) (4)

IND 130707 was submitted May 27, 2016, for a fixed-dose combination (FDC)¹ tablet of bempedoic acid (180 mg) and ezetimibe (10 mg). An EOP2 meeting was requested March 15, 2017, granted March 24, 2017. Preliminary responses were issued May 15, 2017, which the firm accepted as the final minutes, and the meeting was subsequently cancelled.

A pre-NDA chemistry, manufacturing and controls (CMC) meeting, for both applications, was requested May 21, 2018, granted May 31, 2018, and written responses issued August 1, 2018. Initial agreement letters for the pediatric study plans (iPSPs) issued May 4, 2016, for bempedoic acid and January 11, 2018, for the FDC.

The pre-NDA meeting request includes the following proposed indication for the initial submission:

(b) (4)

According to the meeting package submitted June 29, 2018, the firm has revised the proposed indication as follows:

(b) (4)

The firm is proposing to submit 2 NDAs simultaneously: one for the bempedoic acid tablet and one for the FDC tablet. The NDA for bempedoic acid will contain results from the following Phase 3 studies:

- 1002-040: *A Randomized, Double-Blind, Placebo-Controlled, Multicenter Long-Term Safety and Tolerability Study of ETC-I 002 in Patients with Hyperlipidemia at High Cardiovascular Risk Who are not Adequately Controlled by Their Lipid-Modifying Therapy.*
- 1002-046- *A Randomized, Double-Blind, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg compared to Placebo Added to Background Lipid-Modifying Therapy in Patients with Elevated LDL-C who are Statin Intolerant*

¹ Although the preferred description is “fixed-combination drug product” (FCDP), this document will use the term FDC for consistency with the firm’s background package.

- 1002-047- *A Long-term, Randomized, Double-blind, Placebo-controlled, Multicenter study to evaluate the Efficacy of bempedoic acid (ETC-1002) in Patients with Hyperlipidemia at High Cardiovascular Risk not Adequately Controlled by Their Lipid-Modifying Therapy*
- 1002-048- *A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic acid (ETC-1002) 180 MG/DAY As Add-on to Ezetimibe Therapy in Patients with Elevated LDL-C on Low Dose or less than Low Dose Statins*

The FDC tablet NDA will largely reference the monotherapy NDA, but will also contain results from Study 1002FDC-053, titled, *A Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of Bempedoic Acid 180 mg + Ezetimibe 10 mg Fixed-Dose Combination Compared to Bempedoic Acid, Ezetimibe, and Placebo Alone in Patients Treated with Maximally Tolerated Statin Therapy*.

Bempedoic acid tablets and the FDC tablets are intended for once daily oral chronic therapy.

Following the initial approval, the firm is proposing to submit the results from protocol 1002-043, titled, *A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Effects of Bempedoic Acid (ETC 1002) on the Occurrence of Major Cardiovascular Events in Patients with, or at high risk for, Cardiovascular Disease who are Statin Intolerant* (b) (4)

2.0 DISCUSSION

The firm's questions and Company Position are in regular text, followed by our **bolded** responses.

Nonclinical

Question 1

Does the Division agree that the nonclinical data package adequately supports submission of both the bempedoic acid NDA in accordance with 505(b)(1) and the FDC NDA in accordance with 505(b)(2), respectively?

Company Position:

The pharmacology, PK, toxicokinetic, absorption, distribution, metabolism, and elimination properties, and the drug-drug interaction potential of bempedoic acid are fully characterized based on completed nonclinical studies (Section **Error! Reference source not found.**).

Nonclinical studies to evaluate the safety of bempedoic acid have been conducted in mice, rats, rabbits, and monkeys (Section 6.4).

APPEARS THIS WAY ON
ORIGINAL

At the EOP2 Meetings, the Division indicated agreement on the overall nonclinical program for both NDAs but also recommended that the Sponsor conduct the following studies:

Bempedoic acid: 13-week monkey repeat dose safety study (bempedoic acid + atorvastatin) (draft protocol was numbered 1002-500-060; however, the study results will be reported under RR 1002-500-065)

FDC: 13-week rat repeat dose safety study (bempedoic acid + ezetimibe) (dose ranging study (b) (4) RR 1002-500-061)

FDC: Embryo-fetal development rat study (bempedoic acid + ezetimibe) (dose ranging study (b) (4) RR 1002-500-062)

Data from these studies will be provided in the NDA. Based on the results of previous, ongoing, and planned nonclinical studies, the Sponsor considers there will be no unresolved issues or topics relating to the nonclinical development program and that these studies will be adequate to support submission of NDAs for bempedoic acid and the FDC in adults.

Please note that, as mentioned in Section **Error! Reference source not found.**, a second Juvenile Toxicity Study is planned to incorporate the Division's request provided to the Sponsor on 20 December 2017. This study will be ongoing at the time of the NDA submissions; however the protocol will be submitted in advance to the IND. It is not anticipated that the conduct of this study will alter the overall agreed upon PSP studies and timelines.

APPEARS THIS WAY ON
ORIGINAL

FDA Response to Question 1: Your nonclinical program appears to be acceptable to support submission and allow review of the NDAs for bempedoic acid alone and the FDC product (bempedoic acid acid/ezetimibe). However, final determination of the adequacy of the data will be made upon review of the NDAs.

Clinical

Question 2

Does the Division agree that the proposed clinical data package for the bempedoic acid program is adequate to support submission of an NDA for a LDL-C lowering indication for traditional approval in accordance with 505(b)(1)?

Company Position:

The Sponsor is seeking confirmation that the bempedoic acid NDA is ready for submission from the Division's perspective. Furthermore, the Sponsor seeks reconfirmation of the regulatory pathway for traditional approval for an LDL-C lowering indication.

To support our position previously, we provided a summary of the purported mechanism of action of bempedoic acid, the results of a Mendelian randomization study to explore ACL as a therapeutic target, and a recent meta-regression analysis showing that LDL receptor upregulation may be important with respect to predicting whether an LDL-C-lowering drug will reduce the risk for CV events.

All 15 Phase 1 and 10 Phase 2 studies that were committed as part of the development plan will be completed prior to the NDA submission. These studies provide clinical data from >1500 patients who received ≥ 1 dose of bempedoic acid (as monotherapy or in combination with statins and/or ezetimibe) at doses ranging from 2.5 to 240 mg/day. These studies included a broad

range of patient populations, including those with hyperlipidemia, some of whom also reported diabetes, coronary heart disease, or hypertension, and patients unable to tolerate currently available statin medications (**Error! Reference source not found.**). A summary of Phase 2 study results was provided in the briefing document for the 07 February 2017 Type A Meeting.

APPEARS THIS WAY ON
ORIGINAL

The Phase 3 studies are listed in **Error! Reference source not found.** These studies allow for evaluation of the benefit: risk ratio of bempedoic acid and the FDC in relevant high-risk patient populations. Comprehensive Phase 3 LDL-C lowering efficacy studies include patients who are on maximally tolerated statin therapies and require further LDL-C lowering as well as patients where maximally tolerated statins may mean no statin at all. In addition, 1 Phase 3 study and 1 Phase 2 study provide evidence of efficacy in combination with ezetimibe (co-administration) (Study 1002-048) or PCSK9 inhibitor (co-administration) (Study 1002-039).

APPEARS THIS WAY
ON ORIGINAL

The Sponsor has completed 3 (studies 1002-040, 1002-046, and 1002-048) of the 4 planned controlled Phase 3 studies including the largest and longest study conducted with bempedoic acid in patients receiving a maximally tolerated dose of a statin. The completed studies include approximately 2800 of the 3600 patients enrolled in the entire Phase 3 program of controlled studies with bempedoic acid. The data from these completed Phase 3 studies are provided individually in Section **Error! Reference source not found.** The final long-term controlled study with bempedoic acid (1002-047) will complete in 3Q2018, and the data will be included in the NDA. As noted in the Response to Questions on the Content and Format submitted on 22 June 2018, a complete ISS and ISE will be provided in the bempedoic acid NDA. Additionally, as noted in the response, revised integrated Statistical Analysis Plans for the ISS and ISE will be submitted to the IND prior to the pre-NDA meeting.

APPEARS THIS WAY ON
ORIGINAL

Collectively, the data from these studies support a positive risk/benefit profile of bempedoic acid (Question 8). These data to date show that bempedoic acid has a consistent effect across studies and is effective in combination with statins (low, moderate, and high intensity) or ezetimibe or PCSK9 inhibitors, and is well-tolerated. Safety data up to 52 weeks of exposure shows bempedoic acid is safe in the proposed patient population. Confirmation of the size of the safety data base is requested in Question 3.

Key conclusions from the data to date are:

- Bempedoic acid is safe and effective as an add-on combination therapy in hyperlipidemia patients, including high-risk patients, on approved LDL-C lowering monotherapies, including maximally tolerated statins (which may mean no statin at all) or ezetimibe or PCSK9 inhibitors, who require additional LDL-C lowering.

- Once daily treatment with bempedoic acid resulted in statistically significant reductions in LDL-C at Week 12 (primary endpoint) compared with placebo in 3 randomized controlled Phase 3 trials to date.

- Statistically significant reductions in LDL-C at Week 24 compared with placebo were observed in the 2 Phase 3 trials that examined this endpoint.

- The statistical significance of the overall treatment benefit of bempedoic acid at Week 12 was also observed across all key secondary endpoints: non-HDL-C, TC, apo B, and hsCRP (p <0.001 for each).

Statistically significant reductions in LDL-C at Week 52 compared with placebo were observed in Phase 3 Study 1002-040.

Bempedoic acid treatment was well-tolerated and no new safety signals were detected compared with placebo.

The Sponsor expects the data from ongoing studies with bempedoic acid and the FDC will be consistent with data from completed studies. In addition to the LDL-C lowering studies, the Sponsor is conducting a large Phase 3 CVOT with over 12,600 patients planned to enroll. Results of this event-driven study will be submitted in a separate NDA approximately 2 years following approval of the initial indication. The Data Monitoring Committee continues to evaluate the ongoing Phase 3 program quarterly in an unblinded fashion and will continue to evaluate the CVOT after submission of the 2 NDAs.

Both NDA submissions are planned at the end of December 2018/early January 2019. All clinical commitments made with the FDA during the development of this program will be complete at the time of submission and will constitute a complete NDA for the Division's review (see **Error! Reference source not found.** for Table of Clinical Trials). The 120-day Safety Update will be provided 16 weeks after the NDA submission and will provide follow-up data on >1400 patients who are being followed in the long-term open-label extension study to support both the bempedoic acid and FDC submissions (Question 4).

APPEARS THIS WAY ON
ORIGINAL

Based on prior discussions with the Division, the Sponsor understands that the NDA will be reviewed for a traditional approval, consistent with other drugs the Division has approved for LDL-C lowering indications. The FDA provided clear guidance at the Type A meeting that the Phase 3 program would provide an adequate safety database to assess risk for an approval based on LDL-C. From an efficacy perspective, the Division did not recommend designing and conducting additional studies if data from ongoing trials could be provided to support efficacy in combination with statins or ezetimibe or PCSK9 inhibitors.

Overviews of the Quality, Nonclinical, and Clinical Programs are described in Section 6.3, Section 6.4, and 6.5, respectively. The Sponsor seeks the Division's agreement that the proposed data package is sufficient to support submission of an NDA for bempedoic acid, and that the application will be reviewed under the traditional approval pathway for an LDL-C lowering indication (b) (4)

FDA Response Question 2:

Clinical

The data you propose to submit appear to be adequate to support filing of the bempedoic acid NDA for an LDL-C lowering indication. At this time, the Agency has not made any changes to policy regarding the approval pathway for LDL-C-lowering drugs since the approval of evolocumab and alirocumab.

Clinical Pharmacology

Yes, we agree that the proposed clinical pharmacology data package for the bempedoic acid program is adequate to support submission of an NDA in accordance with the 505(b)(1) pathway. However, we have the following additional comments:

- At the End-of-Phase 2 (EOP2) meeting for IND 106654, you reported that the impact of the active metabolite of bempedoic acid on CYP450 enzymes or OATP transporters has not been assessed and that you plan to conduct a study to understand the mechanism of drug interaction. Clarify whether these study/studies have been conducted.

(b) (4)

- Study 1002-016 evaluated the effect of food on the pharmacokinetics (PK) of bempedoic acid tablets. Provide clarification as to whether the to-be-marketed drug product of bempedoic acid tablets was used in the study.
- Ensure that information pertaining to the bioanalytical methods used to quantify bempedoic acid and the active metabolite (ESP15228) such as summary of validation, validation reports, bioanalytical reports for individual studies are included in the NDA submission.
- For the population PK analysis, the following are the general expectations for submitting the pharmacometric data and models:
 - All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
 - A model development decision tree and/or table which gives an overview of modeling steps.
 - For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.
 - In terms of where the code and data should be submitted, the following folders can be used as one example for population PK related codes and data. The codes should be submitted under "module5/datasets/poppk/analysis/programs/" folder (such as run1.ctl.txt, run1.lst.txt, plot1.R.txt) with a define pdf file to explain the role of each file and sometimes with a pdf file as the revieweraid.pdf to explain the flow of running the code if necessary. The datasets should be submitted under

"module5/datasets/poppk/analysis/datasets/" folder (such as poppk.xpt, pkpd.xpt) with a define pdf file to explain the variables within each data file.

Statistics

- 1. In order for us to be able to reproduce your results, at the time of submission, please provide the names of the datasets and programs that were utilized to produce all major tables and results. Please incorporate this information in the footnote of each table. Also, please include comments and clarifications in your programs codes.**
- 2. At the time of submission, we recommend that you include graphical visualization of relationship between adverse events and treatment duration. Suggestions and ideas for graphs of adverse events are provided on CTSPEDIA website <https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome>**

Question 3

Does the Division agree that the proposed clinical and nonclinical data package for the bempedoic acid-ezetimibe FDC program is adequate to support submission of an NDA for a LDL-C lowering indication in accordance with 505(b)(2)?

Company Position:

The Sponsor is seeking confirmation that the bempedoic acid-ezetimibe FDC NDA is ready for submission from the Division's perspective and will support full approval of an LDL-C-lowering indication, assuming the data support a positive risk-benefit assessment. The Sponsor will have completed the nonclinical studies requested at the Type B Meeting, 17 May 2017 specific to the bempedoic acid-ezetimibe FDC; a 91-day oral toxicity study in combination with ezetimibe in rats (Study RR-1002-500-061) and a combination embryo-fetal development study in rats (Study RR-1002-500-062). In addition, all 4 clinical studies agreed between the Sponsor and the Division will be completed by the NDA submission; BA Study 1002FDC-034 with ezetimibe, food effect Study 1002FDC-055, Phase 1 drug-drug interaction Study 1002FDC-049, and Phase 3 Study 1002FDC-053 conducted in patients receiving maximally tolerated statins. After completion of Study 1002FDC-034 it was agreed with the Division (FDA Correspondence, 19 January 2018) (b) (4) if the FDC was compared with its individual components and placebo in Study 1002FDC-053. The clinical study report for Study 1002FDC-034 was provided to IND 130707 on 01 February 2017; data from the remaining ongoing studies will be included as part of the NDA submission. These studies will complete all clinical commitments made with the FDA during the development of this program and constitute a complete NDA for the Division's review (see **Error! Reference source not found.** for Table of Clinical Trials). The Sponsor is seeking confirmation that the Division agrees with this interpretation of our readiness to submit the FDC NDA concurrently with the bempedoic acid NDA.

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FDA Response to Question 3:

Clinical

Yes, we agree that the proposed clinical package for the bempedoic acid-ezetimibe FDC program is adequate to support submission of an NDA.

Clinical Pharmacology:

Yes, we agree that the proposed clinical pharmacology data package for the bempedoic acid-ezetimibe FDC program is adequate to support submission of an NDA in accordance with the 505(b)(2) pathway. However, we have the following additional comments:

- **Study 1002FDC-055 evaluated the effect of food on the PK of the FDC tablets. Provide clarification as to whether the to-be-marketed drug product of the FDC tablet was used in the study.**
- **Ensure that information pertaining to the bioanalytical methods used to quantify bempedoic acid, the active metabolite (ESP15228), and ezetimibe (such as summary of validation, validation reports, and bioanalytical reports for individual studies) are submitted with the NDA.**

Statistics

See the comments provided for Question 2.

Question 4

(b) (4)

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FDA Response to Question 4: Final labeling will depend on review of the data from your development program. The indication should be written to include the necessary information needed to clearly convey the patient population and the conditions of use for which there is substantial evidence that the drug is safe and effective. See the July 2018 draft Guidance for Industry, *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*, for additional considerations.

Question 5

Does the Division agree that the proposed size of the safety database and the relevant durations of exposure at the time of initial NDA submission are sufficient to support the proposed LDL-C lowering indications for both the bempedoic acid and the FDC NDAs?

Company Position:

The core Phase 3 program for the bempedoic acid NDA consists of 4 registration studies (1002-040, 1002-046, 1002-047, and 1002-048) that enrolled more than 3600 patients. In particular, Studies 1002-040 and 1002-047 consist of approximately 3000 patients treated in randomized, double-blind fashion for 52 weeks with in a 2:1 ratio for bempedoic acid and placebo. In addition, Study 1002-050 is an open-label extension study that will ultimately provide data on >1400 patients treated with bempedoic acid ranging from 1.5 to 2.5 years (patients with 2.5 years treatment includes two thirds of the patients who were randomized to bempedoic acid for 52 weeks in the parent study, 1002-040). This open-label study will complete in 2019.

In the Type A Meeting Minutes held on 07 February 2017, the Division confirmed that the proposed size of the safety database at the time of the NDA submission would provide sufficient data to review the safety profile of bempedoic acid based on the Sponsor's estimate that 1620 patients will be exposed to the to-be-marketed dose of bempedoic acid for 12 months in the randomized placebo-controlled studies. As of June 2018, 3 of 4 studies have been completed, and an estimated exposure to bempedoic acid at the time of the NDA submission is provided in Table 1. The Sponsor anticipates a small amount of attrition during the remainder of the ongoing Study 1002-047, but the final number of patients treated with bempedoic acid in the double-blind studies for 12 months will be at least 1500. This exposure number is similar to the recent BLA submissions for drugs in the PCSK9 inhibitor class for LDL-C lowering in high-risk CV hyperlipidemia patients. The Sponsor is seeking the Divisions reconfirmation that the overall size of the safety database is sufficient to support the initial NDA for the LDL-C lowering indications.

Table 1: Estimated Number of Patients Exposed to Bempedoic Acid at Time of NDA Submission

Duration	Estimated Number of Patients Exposed to Bempedoic Acid From Double-Blinded Phase 3 Studies^a
≥ 12 weeks (80 days)	2205
≥ 24 weeks (165 days)	1847
≥ 9 months (265 days)	1614
≥ 12 months (355 days)	1564

^a Phase 3 studies include 1002-040, 1002-046, 1002-048 and 1002-047 (ongoing). Final data from 1002-040, 1002-046 and 1002-048 were used and blinded data with a cutoff of 27 May 2018 was used for 1002-047 and assumes no further dropouts.

In addition to the studies supporting the bempedoic acid program, Study 1002FDC-053 is a Phase 3 study where patients with hyperlipidemia at high CV risk will receive the bempedoic acid-ezetimibe FDC for 12 weeks. A total of 382 patients are randomized into this ongoing study, which is the pivotal study supporting the FDC NDA.

As agreed in the Agency's Information/Advice Letter dated 01 May 2018 in response to the Sponsor's Content and Format document submitted on 05 February 2018 (IND 106654, the Sponsor plans to submit one 120-day Safety Update 16 weeks after submission of the NDA that will support both the bempedoic acid and FDC submissions. There is 1 ongoing study, the open-label long-term extension study, 1002-050 (the data cutoff date for the 120-day Safety Update will be 31 January 2019). The approximate numbers of patients to be included in the NDA and 120-day Safety Update are provided in Table 2.

Table 2: Duration of Treatment with Bempedoic Acid From Study 1002-050 at the Time of NDA and 120-day Safety Update

Time Point	Clinic Visit			
	Week 12	Week 24	Week 52	Week 78
NDA Submission	1400	1400	460	24
120-Day Update	1400	1400	1375	150

In summary, the Sponsor's position is that a robust safety data set will be provided in the 2 NDAs, and that the overall Phase 3 LDL-C lowering program will provide an adequate safety database and overall extent of exposure to assess product safety risk for the Agency's review of the NDAs for LDL-C lowering indication via the traditional approval pathway.

FDA Response to Question 5: The proposed size of the safety database and the relevant durations of exposure at the time of initial NDA submission appear reasonable to support NDA filing and review. If our review identifies uncertainties or additional safety concerns, additional clinical data might be required to evaluate these signals.

Question 6

The Sponsor submitted a Response to Questions document to the Division's Content and Format Advice/Information Request letter. Does the Division confirm agreement with how the Sponsor has proposed to incorporate/address the feedback specifically regarding the Integrated Summary of Safety, Integrated Summary of Efficacy and Integrated Statistical Analysis Plans?

Company Position:

On 05 February 2018, the Sponsor requested the Division's feedback regarding the acceptability of the proposed content and format of the NDAs for bempedoic acid and FDC.

The Sponsor would like to thank the Division for providing comments and recommendations on 01 May 2018. Based on this feedback, the Sponsor is preparing revisions to the Statistical Analysis Plans for the Integrated Summary of Safety and Integrated Summary of Efficacy. A formal Response to Questions was submitted to the Division on 22 June 2018 (IND 106654 and IND 130707) and is provided as an attachment to this document in **Error! Reference source not found.** It describes how the Sponsor plans to incorporate the Division's recommendations. Revised Statistical Analysis Plans are planned for submission in August 2018.

APPEARS THIS WAY
ON ORIGINAL

FDA Response to Question 6: Your plan appears reasonable.

Safety

Question 7

Does the Division agree that bempedoic acid does not have any potential for abuse and that no further assessments will be required for the NDA submissions?

Company Position:

The Sponsor's assessment is that there is no potential for abuse with bempedoic acid because it is not associated with abuse-related activity and is not active in the central nervous system (CNS). This conclusion is based on the following:

- The absence of abuse-related clinical signs in the safety pharmacology, repeat dose safety, and long-term carcinogenicity studies during dosing and recovery phases.
- The negative findings in an in vitro CNS-active site receptor binding study.
- Bempedoic acid drug product and its manufacturing process do not contain any chemicals included in the US Drug Enforcement Administration (DEA) List I of chemicals designated within the Controlled Substances Act, 21 United States Code (USC) §802, Definition 34 (list I) and 35 (list II). The bempedoic acid drug substance manufacturing

(b) (4)

- The lack of evidence to date from Phase 2 clinical safety data (n = 1043 treated patients of which 695 were treated with bempedoic acid) that bempedoic acid produces abuse-related psychoactive effects, such as mood or cognitive changes or withdrawal symptoms, at doses of 180 mg for up to 12 weeks.
- Data from Phase 3 Study 1002-040 (n = 1487 patients who received bempedoic acid) showed no evidence that bempedoic acid produces abuse-related psychoactive effects, such as mood or cognitive changes, at doses of 180 mg for up to 52 weeks based on a search of preferred terms under the MedDRA System Organ Class of Nervous System Disorders and Psychiatric Disorders as well as all preferred terms in the MedDRA Standard Medical Query of Drug abuse, dependence and withdrawal. Under this comprehensive approach, all abuse-related preferred terms suggested for evaluation in the Guidance for Industry (see Section V.B. Abuse-Related Adverse Events in Clinical Safety and Efficacy Studies) were assessed.

For the bempedoic acid-ezetimibe FDC, the Sponsor's assessment is that there is no potential for abuse of bempedoic acid for the reasons stated above. Ezetimibe is currently marketed, not considered active in the CNS, and is not a scheduled drug (Drug Enforcement Administration, 2018; Ezetimibe (Zetia USPI, 2013)). Because of this, the FDC is not expected to have abuse potential.

Data for preclinical and Phase 2 studies described above have already been submitted to IND 106654, and will also be included in the NDA along with data from Phase 3 studies.

Based on physical chemistry properties, the animal safety pharmacology, repeat dose safety and 2-year carcinogenicity, in vitro CNS-target data, and Phase 3 clinical data reviewed above, bempedoic acid has not demonstrated abuse-related activity and is not considered active in the CNS and therefore has no likelihood of abuse-potential. Therefore, additional abuse-potential studies are not considered necessary.

FDA Response to Question 7: We agree that bempedoic acid does not appear to have potential for abuse based on our review of your non-clinical data.

Question 8

The Sponsor recognizes that the final determination of the benefit:risk profile of bempedoic acid will be based on a full review of the data included in the 2 NDA submissions and that the benefit:risk profile will be continually re-evaluated as new data become available. Based on the Sponsor's assessment of the efficacy and safety data available to date, the Sponsor's position is that a REMS is not required. Does the Division agree with the Sponsor's plan to not submit a REMS proposal in the NDAs?

Company Position:

Based on the data from the Phase 1, 2, and 3 studies to date, no safety findings have been observed that would meet the requirements for a REMS (US FDA, 2017b). Bempedoic acid has been administered to over 6000 patients in Phase 1, 2, and 3 studies and has demonstrated a favorable benefit:risk profile. In particular, the most recently completed Phase 3 studies

(1002-040, 1002-046, and 1002-048) show that treatment with bempedoic acid was safe, with a safety profile comparable to placebo (Section **Error! Reference source not found.**, Section **Error! Reference source not found.**, and Section **Error! Reference source not found.** respectively).

To date in the clinical program, adverse events typically associated with statin therapy (e.g., small liver function test elevations, skeletal muscle events, neurocognitive effects, and new onset or worsening of diabetes) were reported in similar percentages of patients in the bempedoic acid and placebo treatment groups. AESIs based on nonclinical experience with bempedoic acid (metabolic acidosis and hypoglycemia) were also reported similarly in both treatment groups. Based on clinical experience with bempedoic acid in Phase 2 studies, uric acid and hemoglobin were closely monitored in the Phase 3 studies. Modest consistent changes in uric acid, hemoglobin, and creatinine occurred during the studies. The modest changes in laboratory values did not precipitate into laboratory-associated adverse events in the high-risk patient populations investigated in these studies. Laboratory values and any associated potential adverse events will continue to be assessed.

No new signals have been observed that have not been previously reported for the cholesterol lowering class of drugs. Consequently, the Sponsor proposes that the potential risks can be adequately mitigated through labeling and routine and active pharmacovigilance as follows:

- The potential risks and conditions of use of the product will be clearly defined in labeling.
- Data from the ongoing open-label extension Study 1002-050 and the CVOT (Study 1002-043) will provide additional safety data to inform post-approval labeling changes. Study 1002-050 will provide data on 1426 patients treated with bempedoic acid for 78 weeks, with two thirds of these patients (those who received bempedoic acid for 52 weeks in Study 1002-040) receiving bempedoic acid for 2.5 years. The CVOT study will also be ongoing at the time of the NDA submission and review process. This is a double-blind outcomes study that will provide data on an additional 12,000+ patients treated for an estimated mean of 3.75 years. This study will be monitored closely by a DMC throughout its duration.
- Routine pharmacovigilance will be conducted in order to identify any newly-emergent adverse events

Based on the evaluation of data from the overall clinical program to date and the criteria necessitating a REMS, the Sponsor is seeking the Division's agreement that a REMS proposal will not be required at the time of the NDA submissions.

FDA Response to Question 8: We agree that a REMS proposal will not be required with your NDA submission. We will determine the need for a REMS during the review of your application.

2 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our May 31, 2018 communication granting the clinical pre-NDA 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
<https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>.

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-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* 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 Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

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](#) and [Pregnancy and Lactation Labeling Final Rule](#) 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 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* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

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: <http://www.fda.gov/ectd>.

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 <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>.

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*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

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.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency’s interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA’s finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a “bridge”

(e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication A</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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/

KATI JOHNSON
08/28/2018