CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216956Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 125154

MEETING PRELIMINARY COMMENTS

Arena Pharmaceuticals, Inc.
Attention: Monique Small, PharmD
Senior Director, Global Regulatory Strategy
6154 Nancy Ridge Drive
San Diego, CA 92121

Dear Dr. Small:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for etrasimod (APD334) tablets.

We also refer to your February 28, 2022, correspondence, received February 28, 2022, requesting a meeting to discuss your planned new drug application (NDA).

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 (240) 402-4276 or email me at kelly.richards@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

Kelly Richards, RN, MSN, RAC
Senior Regulatory Health Project Manager
Gastroenterology
Division of Regulatory Operations for
Immunology and Inflammation
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 7, 2022, from 3:00 pm to 4:00 pm ET
Meeting Location: **Teleconference**

Application Number: 125154
Product Name: Etrasimod (APD334) tablets
Indication: Moderately to severely active ulcerative colitis (UC)
Sponsor Name: Arena Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES (tentative)
Office of Immunology and Inflammation
Julie Beitz, MD, Director

Division of Gastroenterology, Office of Immunology and Inflammation
Jessica J. Lee, M.D., M.M.Sc., Director
Joyce Korvick, M.D., M.P.H., Deputy Director for Safety
Juli Tomaino, M.D., M.S., Deputy Director
Joette Meyer, Pharm.D., Associate Director for Labeling
Matthew Kowalik, M.D., Clinical Team Leader
Anna Reed, M.D., M.P.H., Medical Officer

Division of Regulatory Operations for Immunology and Inflammation, Office of Regulatory Operations
Richard Whitehead, M.S., Supervisory Consumer Safety Officer
Kelly Richards, RN, MSN, RAC, Senior Regulatory Health Project Manager

Division of Pharmacology and Toxicology for Immunology and Inflammation
Jackye Peretz, Ph.D., Lead Pharmacologist
Sarah Morgan, Ph.D., Pharmacologist

Office of Translational Science (OTS), Office of Clinical Pharmacology (OCP), Division of Inflammation and Immune Pharmacology (DIIP)
Insook Kim, Ph.D., Clinical Pharmacology Team Leader
Sojeong Yi, Ph.D., Clinical Pharmacology Reviewer

Office of Biostatistics, (OB), Division of Biostatistics III (DBIII)
Paul Imbriano, Ph.D., Team Leader (Acting)
Dapeng Hu, Ph.D., Statistical Reviewer

Office of Surveillance and Epidemiology (OSE), Division of Medication Error Prevention and Analysis (DMEPA)
Idalia E. Rychlik, PharmD., General Health Scientist
Sherly Abraham, R.Ph., Safety Evaluator

Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRM)
Yasmeen Abou-Sayed, PharmD, Team Leader
Courtney Cunningham, PharmD, Reviewer

Office of the Center Director (OCD), Controlled Substance Staff (CSS)
Chad J. Reissig, Ph.D., Supervisory Pharmacologist
Jovita Randall-Thompson, Ph.D., Pharmacologist

Office of Pharmaceutical Quality (OPQ), Division of New Drug Products(ONDP)
Okpo Eradiri, Ph.D., Biopharmaceutics Branch Chief

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 June 7, 2022, from 3:00 pm to 4:00 pm ET via teleconference between Arena Pharmaceuticals, Inc., and the Division of Gastroenterology. 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. 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

Etrasimod (also referred to as APD334) is a selective S1P1,4,5 modulator being developed by the Sponsor as an oral formulation to treat immune-mediated inflammatory disorders including moderately to severely active ulcerative colitis (UC). The Sponsor intends to submit an original NDA for etrasimod for the treatment of (b) (4) moderately to severely active UC in Q3 2022. A meeting was requested with the Division of Gastroenterology to receive feedback on the planned format and content of the NDA. A separate Chemistry, Manufacturing and Controls (CMC) meeting will be requested at a future date.

2.0 DISCUSSION

Question 1: Does FDA agree that the nonclinical data package for etrasimod is sufficient to support review of an approvable NDA for the treatment of moderately to severely active UC?

FDA Response to Question 1:
Yes, the nonclinical data package outlined in the meeting briefing document appears adequate to support a future NDA submission. However, the ultimate determination of the adequacy of the nonclinical studies to support the marketing of your drug product will be assessed during the NDA review.

Question 2: Does FDA agree that the clinical pharmacology and biopharmaceutics data packages, along with associated analytical methods, are sufficient to support review of an approvable NDA for etrasimod for the treatment of moderately to severely active UC?

FDA Response to Question 2:
Yes, the proposed data packages for clinical pharmacology and biopharmaceutics appear reasonable to support your NDA submission. However, the adequacy of the clinical pharmacology and biopharmaceutics information to support the marketing approval will be determined during the NDA review.

We have the following comments:

1. **For biopharmaceutics data in section 2.7.1, add subsections for dissolution method validation as well as development and validation of the analytical method used for dissolution samples; provide a link to the analytical method if it is presented in a different section within the eCTD.**

2. **We note that multiple clinical formulations were developed and used during different phases of your clinical development program. In your NDA submission, specify the formulation that was used in each clinical study in a tabular format. As a general comment, if the to-be-marketed formulation is different from the clinical formulation used in phase 3 trials, the data to establish a bridge between the to-be-marketed formulation and the phase 3 clinical formulation(s) needs to be submitted.**

Question 3: Does FDA agree that the planned presentation of safety data based on the Phase 3 pivotal studies (APD334-301 and APD334-302), including the updates described in the Sponsor Position, are sufficient to support a risk-benefit assessment of etrasimod for the treatment of moderately to severely active UC?

FDA Response to Question 3:
The subject exposure numbers provided in your background package and your plan to expand your definition of adverse events of special interest (AESI) to

include AEs identified by your review of the available data (i.e., "sponsor-designated events of interest [SDEIs]"), appear reasonable. We recommend that you include all available safety data across all indications under investigation as part of the integrated summary of safety with this NDA submission. Ultimately, the risk-benefit assessment will be made during the NDA review.

We note that it is premature to comment on the adequacy of the safety data to obviate the need for first-dose cardiac monitoring in the commercial setting. As stated in the Type C written responses only meeting dated October 29, 2021, whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements would be, will be determined during the NDA review.

Additionally, Section 6.6.1.5 of the ISS statistical analysis plan (SAP) states that risk differences between etrasimod and placebo along with 95% confidence intervals using the Wilson's score method will be presented in the comparative analyses. The integrated analyses should adjust for or be stratified by study. Crude pooling can lead to confounding when the randomization ratio differs between studies. In addition, adjusting for study will increase precision when incidence rates differ across studies. In your future NDA submission, specify the method that will be used to adjust for study in the ISS SAP.

Question 4: Based on the currently available nonclinical data, does FDA agree that these data are sufficient to support the review of the abuse potential of etrasimod and that no further abuse liability studies are needed?

FDA Response to Question 4:
The data and information as summarized in your meeting materials appear adequate to support submission of an NDA for etrasimod. However, our final determination regarding the abuse potential of a proposed drug product will be made following a comprehensive review of all drug abuse potential-related data submitted under an NDA. If significant signals of drug abuse potential are identified beyond the data you summarized (e.g., cases of abuse-related AEs that code to euphoric mood), further abuse-related studies may be needed.

We have the following additional comments regarding the assessment of drug abuse potential:

1. **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 drug abuse potential evaluation and information required at the time of NDA**

submission, see the guidance for industry, *Assessment of Abuse Potential of Drugs* (January 2017).[1]

2. **Submit final study reports on all studies you reference to support your assertions with respect to the abuse potential of etrasimod.**

3. **Additional information is needed to evaluate the drug abuse potential of etrasimod, and we recommend that you conduct a drug abuse-related adverse event (AE) assessment, as outlined below.**

   During all phase 1, 2, and 3 studies, including all completed, ongoing and any future studies, capture AEs that may be indicative of drug abuse potential (e.g., CNS-related, drug abuse-related, etc.) and provide detailed narratives for these AEs. The incidence of these AEs in comparison to placebo in trials should be reported by study, population, and dose, and should be displayed in tabular format, including study number and type of study, subject ID number, narratives, case description and details. Tables should be created for higher level MedDRA terms, even if there were few patients or subjects who experienced a particular AE. In addition, you should provide a list of terms that will prompt these reports, including AE terms such as euphoria, dissociative effects, impaired cognition and attention, psychomotor effects, inappropriate affect, overdose, misuse, or lost or unaccounted for medication and unjustified dose increases.

   Narratives describing these events should be provided, including time to onset in relation to drug administration, duration of the event, dose of drug, severity, medical outcome, and disposition of the subject (e.g., if the AE resulted in discontinuation from the study); also, indicate if more than one event was observed simultaneously, and if other drugs were taken by subjects at the time of the event. In addition, if available, provide pharmacokinetic measures for subjects reporting the event to help assess whether there is a temporal correlation between drug plasma levels and these AEs.

   Refer to section V.B. of guidance for industry, *Assessment of Abuse Potential of Drugs* (January 2017)[1] for additional details and recommendations.

4. **We recommend that you capture any possible cases of abuse (subjects taking the drug for non-therapeutic purposes, e.g., for psychoactive effects such as high or euphoria) in all clinical trials. Additionally, you should look for drug accountability discrepancies (e.g., missing medication, loss of drug, or non-compliance cases in which more investigational drug was**

[1] For the most recent version of a guidance, check the FDA guidance web page at https://www fda.gov/regulatory-information/search-fda-guidance-documents.

used, as compared to expected use). Provide data in tabular form for all reports of abuse, overuse, lost/stolen/missing or unaccounted product that occurred in clinical trials (phase 1, 2 and 3). These data should include study number and type of study, subject ID number, narratives, case description, and other available details.

a. Provide narratives for cases where the patients drop out from studies for reasons that might be coded as "protocol violation," "lack of efficacy" (to eliminate the possibility of aberrant behaviors in patients who drop out of the study supposedly due to lack of efficacy), "lost to follow up," "non-compliance to study medication or procedures," "over compliance," or for "other." Case reports should be provided separately.

b. Report any use of the investigational formulation by individuals other than the patients (family member, health care practitioner, etc.).

c. **Report any instances of drug accountability discrepancies that may have occurred at the study site level and identify the origin of the discrepancy and individuals involved.**

Question 5: Does FDA agree that the submission of financial disclosures from clinical investigators for only Studies APD334-301 and APD334-302 conducted on behalf of Arena Pharmaceuticals, a wholly owned subsidiary of Pfizer, is sufficient for the planned NDA?

FDA Response to Question 5:

We agree with your plan to submit financial disclosure information from clinical investigators for studies APD334-301 and APD334-302; however, we do not agree that financial disclosure information should be limited to Arena Pharmaceuticals. As noted in the guidance for clinical investigators, industry, and FDA staff, *Financial Disclosure by Clinical Investigators* (February 2013)[1], if the sponsor changes during the course of the study or within one year of completion of the study, the clinical investigators will need to update their financial disclosure information relevant to the new sponsor. Therefore, the clinical investigators should update their financial disclosure information as it pertains to Pfizer.

Additional FDA Comments:

Clinical:

1. **We note that you have proposed a secondary endpoint to evaluate the efficacy of etrasimod on "mucosal healing" at Week 12 and Week 52, defined as subjects with an ES of 0 or 1 (excluding friability) and (b) (4) Geboes score of less than 2. We do not agree with the use of the term "mucosal healing" at this time as there is no consensus on a definition of, or scoring system for, histologic resolution of**

mucosal inflammation in subjects who achieved endoscopic remission in UC. If the results of this endpoint are considered appropriate for inclusion in labeling, they will be described using alternative descriptive terminology (e.g., endoscopic-histologic mucosal improvement).

2. **Additionally, in your NDA submission, you will need to include detailed justification for the above proposed secondary endpoint that will incorporate histologic and endoscopic findings, focusing on how achieving these definitions is correlated with improved longer term UC clinical outcomes (e.g., avoiding hospitalization, need for corticosteroids, progression to surgery, etc.). Also include details of how biopsy collection, handling, and reading of histology were standardized.**

3. **Your proposed definition of clinical remission of a SF of 0 (or 1 with a greater than 1-point decrease from baseline), RB of 0, and ES less than or equal to 1 (where 1 excludes friability) at Week 12 and Week 52 is acceptable. However, we recommend that you provide an additional analysis with a definition of clinical remission that is aligned with the Division's current recommended approach: a modified Mayo Score (mMS) of 0 to 2, including a SF of 0 or 1, RB of 0, and ES 0 or 1 (score of 1 modified to exclude friability) at Week 12 and Week 52. Refer to the draft guidance for industry *Ulcerative Colitis: Developing Drugs for Treatment* (April 2022)[2] for further information regarding the Division's recommended endpoint approach.**

Clinical Pharmacology:

1. **Refer to the following FDA guidance[1] for additional information related to population PK and exposure-response analyses:**
   a. *Population Pharmacokinetics* (February 2022)
   b. *Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications* (May 2003)

2. **Refer to the FDA website "Model/Data Format" for pharmacometric data and models submission guidelines, available at** https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/model-data-format.

[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/regulatory-information/search-fda-guidance-documents.

3.0

OTHER IMPORTANT LANGUAGE

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our March 17, 2022, 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.[3]

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

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

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*.[4] 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.

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[5] and Pregnancy and Lactation Labeling Final Rule[6] 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

[4] 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.
[5] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[6] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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.

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)				

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[7] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[8]. 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.

[7] https://www.fda.gov/media/84223/download

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

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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/

KELLY D RICHARDS
05/31/2022 05:21:08 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 125154

MEETING MINUTES

Arena Pharmaceuticals, Inc.
Attention: Mark A. Longer, PhD
VP, Regulatory Affairs & Quality
6154 Nancy Ridge Drive
San Diego, CA 92121

Dear Dr. Longer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for etrasimod (APD-334).

We also refer to the meeting between representatives of your firm and the FDA on October 30, 2018. The purpose of the meeting was to discuss your End-of-Phase 2 (EOP2) 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, call me at (240) 402-4276.

Sincerely,

{See appended electronic signature page}

Kelly Richards, RN, MSN
Captain, U.S. Public Health Service
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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: October 30, 2018 from 9:00am-10:00am ET
Meeting Location: 10903 New Hampshire Avenue
White Oak Building #22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: 125154
Indication: Moderate to severe active ulcerative colitis
Sponsor/Applicant Name: Arena Pharmaceuticals, Inc.

Meeting Chair: Anil Rajpal
Meeting Recorder: Kelly Richards

FDA ATTENDEES

Division of Gastroenterology and Inborn Errors Products (DGIEP)
Jessica J. Lee, M.D., M.M.Sc., Associate Director
Anil Rajpal, M.D., Medical Team Leader
Marjorie Dannis, M.D., Medical Officer
Sushanta Chakder, Ph.D., Supervisory Pharmacologist
Emanuel Akinshola, Ph.D., Pharmacologist *(Via Teleconference)*
Kelly Richards, R.N., M.S.N., Senior Regulatory Health Project Manager

Office of Clinical Pharmacology
Insook Kim, Ph.D., Team Leader, Office of Clinical Pharmacology (OCP),
Division of Clinical Pharmacology 3 (DCP3)
Elizabeth Shang, R.Ph., Clinical Pharmacology Reviewer, OCP, DCP3

Office of Biostatistics
George Kordzakhia, Ph.D., Statistical Team Leader, Division of Biostatistics III (DBIII)
Paul Imbriano, Ph.D., Statistical Reviewer, DBIII

SPONSOR ATTENDEES

Vincent M. Caralli, Senior Director, Regulatory Affairs, Arena
Mark A. Longer, PhD, VP, Regulatory Affairs and Quality Assurance, Arena
Wade DeMond Senior Director, Regulatory CMC, Arena

Giles Hulley Senior Director, Regulatory Affairs, Arena
Caroline Lee, PhD, Senior Director, Nonclinical Development and Clinical Pharmacology, Arena
Kye Gilder, PhD, VP, Biostatistics and Data Management, Arena
John Grundy, PhD, VP, Nonclinical Development and Clinical Pharmacology, Arena
Snehal Naik, PhD, Senior Director, Clinical Development, Arena
Christopher H. Cabell, MD, MHS, Senior VP, Head of Clinical Development, Arena
Preston S. Klassen, MD, MHS, Executive VP, R&D and Chief Medical Officer, Arena
(b) (4)

(Via Teleconference)
William J. Sandborn, MD, Director, Inflammatory Bowel Disease Center, Chief, Division of Gastroenterology, UC San Diego Health Professor of Medicine at the Department of Medicine, UC San Diego School of Medicine Consultant, Clinical Development

1.0 BACKGROUND

Etrasimod (also referred to as APD334, APD334 L-arginine or AR401959) is a selective S1P1,4,5 modulator being developed by the sponsor as an oral treatment option for immune-mediated inflammatory disorders. The sponsor has completed a 12-week phase 2, randomized, double-blind, placebo-controlled study of etrasimod in patients with moderately to severely active ulcerative colitis (UC). To that effect, a Type B, End-of-Phase 2 meeting was requested with DGIEP to obtain feedback on the proposed phase 3 program design and other key objectives related to the start of the phase 3 program and future NDA submission for etrasimod for the treatment of patients with moderately to severely active UC.

FDA sent Preliminary Comments to Arena Pharmaceuticals, Inc., on October 26, 2018.

2.0 DISCUSSION

Nonclinical Pharmacology/Toxicology

Question 1: Does the FDA agree that the data and information from completed, ongoing, and planned nonclinical pharmacology and safety studies of etrasimod, including studies on primary and secondary pharmacodynamics, safety pharmacology, subchronic and chronic toxicology, genotoxicity, reproductive and developmental toxicity, phototoxicity, and carcinogenicity, are sufficient to support conduct of the proposed Phase 3 clinical program, as well as assessment of NDA approvability of etrasimod for the treatment of UC?

FDA Response to Question 1:

No, we do not agree. Although the completed, ongoing and planned nonclinical studies listed in the meeting package appear adequate to support the proposed phase 3 clinical program, you need to conduct a pre- and post-natal developmental study in rats prior to the NDA submission.

Question 2: Does the FDA agree that the data and information from completed, ongoing, and planned nonclinical absorption, distribution, metabolism, and elimination (ADME) studies, together with toxicokinetic data from completed subchronic and chronic toxicity studies in rats and dogs, are sufficient to support conduct of the proposed Phase 3 clinical program, as well as assessment of NDA approvability of etrasimod for the treatment of UC?

FDA Response to Question 2:

Yes, we agree.

Clinical Pharmacology

Question 3: Does the FDA agree that the completed, ongoing and planned clinical pharmacology and biopharmaceutics studies are sufficient to support conduct of the proposed Phase 3 clinical program, as well as assessment of NDA approvability of etrasimod for the treatment of UC?

FDA Response to Question 3:

1. **Depending on the systemic exposure of M3 relative to the parent drug, you should evaluate the effect of M3 on major CYP450 enzymes and transporters, using *in vitro* system as an initial step. If the *in vitro* study results indicate a potential drug-drug interaction (DDI), then an *in vivo* study will be needed. Refer to FDA Guidance for Industry with regard to *in vitro* DDI (https://www.fda.gov/downloads/Drugs/Guidances/UCM581965.pdf).**
2. **If M3 is a major metabolite, you should also characterize the pharmacokinetic (PK) of M3 in patients in your planned phase 3 trials. The PK blood sampling scheme for M3 should be adequate to characterize the PK of M3.**
3. **Your proposed product appears to be a CYP2C8 and CYP2C9 substrate. Effect of the inhibitors and inducers of these two CYP enzymes on the systemic exposures of**

your proposed product need to be evaluated in humans. Similarly, effect of UGT1A7 inhibitors on the systemic exposures to etrasimod should be evaluated.

Meeting Discussion: The sponsor provided details on their initial exposure estimate (see attached document) and sought confirmation from FDA that no further PK assessment of metabolite M3 would be needed if their initial exposure estimate was confirmed.

The sponsor stated that the AUC of M3 will be estimated in phase 1 clinical pharmacology studies. In addition, the sponsor confirmed that the M3 metabolite will be measured in the phase 3 studies. The sponsor clarified that M3 is also found in animal species.

Question 4: Does the FDA agree that clinical drug-drug interaction studies do not need to be completed prior to the start of the planned Phase 3 clinical program?

FDA Response to Question 4:

No, we cannot agree at this time. It is unclear how you plan to address your proposed product as a victim drug as it appears to be a CYP2C8, CYP2C9, and UTG1A7 substrate. If the CYP2C8, CYP2C9, and UTG1A7 inhibitors or inducers are among common concomitant medications for patients with UC, then you should conduct *in vivo* drug-drug interaction studies prior to the start of phase 3 studies. Also see #3 of the response to Question 3.

Meeting Discussion: The sponsor provided their approach (see attached document) to address etrasimod as victim drug and sought agreement from FDA that their proposed approach was acceptable. FDA agreed with the sponsor's approach as presented in the attached document. FDA confirmed that the list of CYP2C8 and CYP2C9 inducers and inhibitors should be included in the protocol. FDA stated that the UTG1A7 inhibitors and inducers should be prohibited.

Question 5: Does the FDA agree that the safety profile and pharmacologic activity observed in completed Phase 1 and Phase 2 clinical studies support the selected oral dose of 2 mg etrasimod once daily (QD) for use in the proposed Phase 3 program for the treatment of UC?

FDA Response to Question 5:

The dosing regimen you have proposed (2 mg etrasimod once daily) appears reasonable for the proposed phase 3 program for the treatment of UC, barring any new safety concerns you identify in ongoing studies of etrasimod. We may have additional comments after you submit your final protocol for review.

<u>Clinical Safety and Efficacy</u>

Question 6: Does the FDA agree that the proposed Phase 3 clinical program designed to evaluate the ability of etrasimod to both induce and maintain clinical remission in patients with UC,

including the proposed primary endpoints for each study, will support assessment of NDA approvability of etrasimod for the treatment of UC?

FDA Response to Question 6:

It appears that you are proposing the following phase 3 studies in the moderately to severely active UC population:

- **Study APD 334-301: 52-week study with treat-through design; and primary endpoint of clinical remission at Week 52**
- **Study APD 334-302: 12-week study with primary endpoint of clinical remission at Week 12**

The following definitions are used above:

- **Moderately to severely active UC is defined as a modified Mayo score of 4 to 9 with an endoscopy subscore of ≥ 2. (Modified Mayo score is defined as the sum of the stool frequency, rectal bleeding, and endoscopy subscores; the Mayo endoscopy subscore is modified so that a value of 1 does not include friability.[1])**
- **Clinical remission is defined as a stool frequency subscore = 0, or = 1 with a ≥ 1-point decrease from baseline; rectal bleeding subscore = 0; and endoscopy subscore ≤ 1 (excluding friability).**

The final decision on the adequacy of your proposed development program for filing and potential approvability of the NDA will be made after you have submitted a complete application. However, we have the following comments:

- **Definition of Moderately to Severely Active UC: We request that you modify the definition of moderately to severely active UC (in the entry criterion for each of the phase 3 studies) to a modified Mayo score of between 5 and 9 and a Mayo endoscopic subscore of ≥ 2 (where modified Mayo score is defined as the sum of the Mayo stool frequency subscore, Mayo rectal bleeding subscore, and Mayo endoscopic subscore; the Mayo endoscopic subscore is modified so that a value of 1 does not include friability).**
- **Design of Study APD 334-301: Your proposed primary endpoint of "clinical remission at Week 52" appears reasonable. However, you should incorporate a plan to assess clinical response at a specified earlier timepoint than Week 52 at which clinical response is expected so that patients who fail to demonstrate clinical response by that timepoint and thus may not benefit from prolonged treatment with etrasimod are either excluded from the study or provided another treatment option. (If an endoscopy is not scheduled at the specified timepoint for assessment of clinical response, you should define clinical response based on non-invasive assessments such as stool frequency and rectal bleeding.) As an alternative to your proposed primary endpoint of "clinical remission at Week 52" and proposed first-ranked secondary endpoint of "induction of clinical remission at Week 12", we recommend you consider co-primary endpoints of clinical remission at Week 12 (or a later timepoint when you expect a large proportion of patients to achieve remission) and of clinical remission at Week 52 (each endpoint tested at the population level). In addition, we recommend that you consider including**

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a highly-ranked secondary endpoint of "sustained remission" which should be defined as clinical remission at both Week 12 and Week 52 (at the patient level) in order to characterize the durability of response beyond the induction period; although final decisions on labeling language would be made at the time of NDA review, our current thinking is that you would have to meet this secondary endpoint to support a "sustained remission" claim. Further, we recommend that you incorporate assessments of clinical response (based on non-invasive assessments such as stool frequency and rectal bleeding) at timepoints between Week 12 and Week 52 assessments to strengthen the evidence that patients are able to sustain remission.

In addition, we have the following comments regarding your proposed secondary endpoints:

- **"Symptomatic remission": It appears that you are proposing "symptomatic remission" as a stool frequency subscore = 0, or = 1 with a ≥ 1-point decrease from baseline; and rectal bleeding subscore = 0. We recommend that you revise your proposed secondary endpoint of "symptomatic remission" to the following: Mayo stool frequency subscore = 0, and Mayo rectal bleeding subscore = 0. However, we cannot agree at this time that this endpoint, if met, would support a labeling claim of "symptomatic remission."**
- **"Corticosteroid-free remission": It appears that you are proposing "corticosteroid-free remission" as "symptomatic remission" at Week 52 with ≥4 weeks corticosteroid free. We recommend that you revise your proposed secondary endpoint of "corticosteroid-free remission" so that it is based on "clinical remission" instead of "symptomatic remission". Also, provide your rationale for the proposed 4-week minimum duration over which a patient is considered to be both corticosteroid-free and in remission; we recommend that you consider a longer duration (e.g., 12 weeks).**
- **"Mucosal healing". (b) (4) It appears that you are proposing each of these endpoints as follows:**
  - **"mucosal healing": endoscopy subscore of ≤ 1 (excluding friability) with histologic remission (Geboes index score < 2.0),**

(b) (4)

(b) (4) **"mucosal healing",** (b) (4) **We request that you provide information to support the proposed scoring system (Geboes index) as well as the specific cutoff scores used in the proposed endpoint definitions. If these proposed endpoint definitions are consistent with professional society consensus opinion, please submit the consensus opinion that your definition was based upon for our review. If a consensus opinion does not exist, provide evidence to support the definition you have proposed, including how it correlates with disease activity assessments, and preferably, meaningful clinical outcomes. If different definitions exist in the literature/clinical practice (e.g., the field has not identified a single community-supported definition), please also provide a detailed rationale for your selection of your proposed definition, its strengths, and its limitations.**

Meeting Discussion: The sponsor proposed a definition of moderately to severely active UC as defined by a Modified Mayo score (MMS) of 4 to 9 that includes an endoscopy subscore (ES) ≥ 2 and rectal bleeding (RB) subscore ≥ 1. The sponsor indicated that excluding patients with a MMS of 4 would decrease the potential enrollment by approximately 10%. With inclusion of the criterion of RB subscore of ≥1, a sufficiently symptomatic population would be selected because RB is more specific to UC than stool frequency.

FDA stated that with the proposed incorporation of RB score of ≥ 1, the MMS of 4-9 is reasonable as inclusion criterion. The sponsor agreed to conduct a sensitivity analysis of the inclusion criteria of moderate to severe UC (defined as MMS of 5-9 with ES ≥ 2).

FDA stated the proposed approach for defining corticosteroid-free remission (see attached document) was acceptable.

The sponsor agreed to assess response (based on non-invasive measures) between Week 12 and Week 52.

The sponsor agreed to incorporate coprimary endpoints at Week 12 and Week 52 at the population level.

The sponsor agreed to consider incorporating sustained remission at Week 12 and Week 52 (at the patient level) as a highly ranked secondary endpoint.

Question 7: Does the FDA agree with the proposed measures and associated plans for monitoring and assessing cardiac, pulmonary, and ophthalmic safety of subjects participating in the etrasimod Phase 3 program?

FDA Response to Question 7:

It appears that the safety assessments that you are proposing to conduct in the etrasimod phase 3 program include the following:

- **<u>Cardiac</u>: A 3 hour post-dose cardiac safety monitoring plan [i.e., ECG's and vital signs at Screening, Pre-dose (Baseline), and 3 hours Post-dose] with criteria for discontinuation and provisions for conducting an ECG (each of these based on HR, SBP, and symptoms) and provisions for release from vs. remaining in the clinic (based on HR, SBP, and ECG findings). The Day 1 safety ECG will be repeated if a subject has a dose interruption of ≥ 2 weeks. (Section 11.4.3 of the Meeting Package)**
- **<u>Pulmonary</u>: Routine pulmonary function testing (PFT) will not be conducted using spirometry. Spirometry including measures of forced vital capacity (FVC), forced expiratory volume in the first second (FEV1) and mean forced expiratory flow between 25% and 75% of FVC (FEF25-75%) will be performed when clinically indicated and in conjunction with the respective inclusion/exclusion criteria. (Section 11.4.4 of the Meeting Package)**
- **<u>Ophthalmic</u>: For patients with no prior ocular comorbidities, visual acuity testing and a visual system questionnaire will be performed at Screening and at Week 12, with provisions for optical coherence tomography (OCT; to be interpreted by an**

ophthalmologist) in the event of a change in visual acuity in order to rule out and monitor for any significant retinal disease. For patients with uncontrolled diabetes or diabetes with significant comorbidities, or patients with history of uveitis or ocular comorbidities, evaluation by an ophthalmologist (supported by OCT at sites where available) will be conducted at Screening and at Week 12 to rule out and monitor for any significant retinal disease. (Section 11.4.5 of the Meeting Package)

We have the following comments regarding your proposed cardiac, pulmonary, and ophthalmic safety monitoring plan:

- **Cardiac: We recommend the addition of 12 lead ECGs hourly through Tmax (as part of first dose monitoring procedures). In the event of an interruption of treatment, first-dose monitoring procedures should be performed after re-initiation of treatment as follows:**
  - **after interruption of ≥ 1 day within the first 2 weeks of treatment**
  - **after interruption of ≥ 7 days during weeks 3 and 4 of treatment**
  - **after discontinuation for ≥ 14 days after the first month of treatment**
- **Pulmonary: To address the concern of pulmonary abnormalities which may occur as a class effect with S1P receptor modulators, we request that you make the following changes:**
  - **include an exclusion criterion for patients with FEV1 or FVC < 70% of predicted values at screening**
  - **include Baseline, 3 month, 6 month, and end of study pulmonary function testing (FEV1, FVC and DLCO) (in Study APD 334-301), and Baseline and end of study pulmonary function testing (FEV1, FVC and DLCO) (in Study APD 334-302)**
  - **include rules for study discontinuation of individual patients with pulmonary adverse events**
- **Ophthalmic: We disagree with your proposal of not conducting OCT unless visual acuity changes are identified. We recommend the addition of an ophthalmologic exam in all patients that includes OCT at baseline, 3-4 months, and end of study (in Study APD 334-301); and at baseline and end of study (in Study APD 334-302).**

We may have additional comments after you submit your final protocols for review.

Meeting Discussion: The sponsor sought additional advice and clarity (see attached document) on supportive information that would justify the adequacy of their proposed safety database for the pre-marketing risk assessment of etrasimod.

The sponsor proposed using a risk-based assessment that is comprised of using a Data Monitoring Committee along with measuring the pulse at a 4-hour timepoint. Provided the HR is >50 an ECG would not be conducted. For a HR of <50, an ECG would be performed.

FDA stated that given the concerns with this class of drugs, a risk-based assessment could not be agreed to at this time. FDA stated they will consider the proposal following a submission provided by the sponsor and respond in a separate advice letter.

FDA reiterated that OCT should be assessed at baseline, 3-4 months, and end of study (in Study APD 334-301); and at baseline and end of study (in Study APD 334-302) because of a lack of available data. The sponsor noted that OCT may not be available in all countries.

FDA stated that if OCT is not available at a particular site, a fundoscopic exam performed by an ophthalmologist may be acceptable provided that it is a small percentage of the study population. The sponsor agreed to provide an estimate of the percentage of the proportion of the study population that may not have OCT available (by region).

Question 8: Does the FDA agree with the proposed comparability plan to support a change in the site of manufacture of etrasimod drug substance during the conduct of the Phase 3 clinical program?

FDA Response to Question 8:

From the API perspective, we agree that the comparability plan to support a change in the site of manufacture of the API during the phase 3 clinical program is reasonable.

In addition, you must address the following biopharmaceutics concerns:
Although demonstration of *in vivo* bioequivalence is not required, we recommended that you provide the following documentation:

<u>Dissolution Documentation:</u>

1. **Provide the solubility data/information on this API.**
2. **Provide a comparison of the Particle size distribution for your APIs manufactured at the two sites.**

3. **Perform a multi-time point *in vitro* dissolution profile in the proposed application/compendial medium at the appropriate time points (as stated in Table 8 P. 43/262 of your submission package) or until an asymptote is reached.**

The comparative dissolution profiles (n=12 test articles/lot) of your drug product manufactured using the proposed and current APIs should be similar (i.e., f2 ≥ 50).

Submit the above comparative dissolution profile data with your justification under this IND to the Agency for review and discussion if the proposed change to API is adequate or not.

Additional CMC Comments:

1. **For your NDA, the drug product specification should be based on the ingredients, solvents, manufacturing process, results of the stability tests of the registration and supportive batches as well as ICH Guidelines Q6 A. The drug product impurities should be listed in specification table as specified, unspecified and total impurities and controlled per ICH Guidelines Q3B. The elemental impurities should be controlled per USP <232>, USP <233> and ICH Q3D.**

2. **Provide validated analytical methods used for the drug product release in accordance with ICH Guidelines Q2 (R1) and demonstrate that they are suitable for the intended use. The tablets must be clearly marked or imprinted per 21 CFR 206.10. The final determination of the drug product specification will be based on the thorough review of the data provided in your NDA.**

3. **Please refer to the following Guidance for Industry for additional CMC information:**

- **INDs for Phase 2 and Phase 3 studies: Chemistry, Manufacturing and Controls; May 2003 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070567.pdf)**

4. **For preparation of the CMC sections in your NDA refer to relevant CDER Pharmaceutical quality/CMC Guidances and ICH Quality Guidelines located at the following websites:**

- **https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm**

- **http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html**

Question 9: Does the FDA agree that the safety databases from the proposed etrasimod Phase 3 clinical program for treatment of UC and a parallel etrasimod Phase 3 clinical program for the treatment of Crohn's disease (CD) can be combined for the pre-marketing risk assessment, and will support assessment of NDA approvability of etrasimod for the treatment of UC?

FDA Response to Question 9:

According to the information you have provided,[2] you estimate that, at the time of NDA submission, exposure to etrasimod will be as follows (at the anticipated dose for intended use):

- **All subjects: 2380 patients overall, 1664 patients for at least 6 months, and 989 patients for at least 1 year**
- **UC patients only: 1012 patients overall, 817 patients for at least 6 months, and 558 patients for at least 1 year**
- **CD patients only: 1077 patients overall, 834 patients for at least 6 months, and 431 patients for at least 1 year**

If you submit an original NDA that encompasses both indications (UC and CD), then it would be reasonable to consider the combined safety database (across both disease populations) for the pre-marketing risk assessment of etrasimod; we note the precedent for use of the combined UC and CD safety database for the pre-marketing risk assessment of

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vedolizumab. We remind you that you should provide safety data by disease population (UC patients, CD patients, UC and CD patients combined, each of the other disease populations, and all patients) and by dose (anticipated dose for intended use, and each of the other doses studied). Further, we remind you that you should ensure sufficient exposure in each of the individual target populations (i.e., sufficient exposure in UC, and sufficient exposure in CD) at the dose for intended use.

We cannot provide agreement at this time that the safety database you have proposed (even if combined for both indications, UC and CD) would be adequate for the pre-marketing risk assessment of etrasimod. We acknowledge that your proposed safety database is significantly larger than the minimum ICH E1A guideline recommendations regarding numbers of patients exposed for the various durations; however, there are exceptional safety concerns surrounding sphingosine 1-phosphate 1 receptor modulators (particularly risk of PML), and there are evolving safety data from studies of your product, studies of other products in the same class (sphingosine 1 phosphate receptor modulators), and postmarketing data for the product in the same class that is currently approved (fingolimod). We request that you provide justification (based on available data with your product as well as other products in the class) that your proposed safety database would be adequate for the pre-marketing risk assessment of etrasimod. We recommend that you request another meeting with us to discuss your proposed safety database.

We also look forward to further discussion once phase 3 data with etrasimod are available. The final decision on the adequacy of the safety database to support approval will be made upon review of the complete application.

For additional information regarding the size and nature of an adequate safety database for a marketing application, we advise that you refer to the FDA Guidance for Industry - *Premarketing Risk Assessment*, located at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm072002.pdf.

FDA ADDITIONAL COMMENTS:

1. **You indicated that you might conduct an interim analysis for sample size re-estimation in study APD334-301. Note that increasing the sample size based on an interim analysis may inflate the type I error rate. Your SAP should include an appropriate statistical adjustment. For an example, see Cui, Hung, Wang (Biometrics 1999).**

2. **Given the reports of cases of PML associated with another drug in the class, the protocols should instruct investigators to withhold study drug and perform an appropriate diagnostic evaluation at the first sign of PML. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.**

3.0 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.

4.0 DATA STANDARDS FOR STUDIES

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

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pd

f), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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

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

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

5.0 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.

6.0 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 the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

7.0 NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

8.0 UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials (available at: https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf) and for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

9.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

10.0 ATTACHMENTS AND HANDOUTS

The document provided by the sponsor is attached.

5 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KELLY D RICHARDS
10/30/2018