CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212526Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119183

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Amber Ying Zhu, MS
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Ms. Zhu:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BYL719.

We also refer to the telecon between representatives of your firm and the FDA on October 16, 2018. The purpose of the meeting was to discuss the safety and efficacy data from the CBYL719C2301 (SOLAR-1) trial and discuss the content for the NDA submission.

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

If you have any questions, call Charlene Wheeler, MSHS, Senior Regulatory Project Manager, at (301) 796-1141.

Sincerely,

{See appended electronic signature page}

Charlene Wheeler, MSHS
Senior Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

{See appended electronic signature page}

Lola Fashoyin-Aje, MD, MPH
Acting Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
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: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: October 16, 2018, 4-5PM
Meeting Location: Teleconference

Application Number: IND 119183
Product Name: BYL719

Indication: Breast cancer
Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Lola Fashoyin-Aje, MD, MPH
Meeting Recorder: Charlene Wheeler, MSHS

FDA ATTENDEES

Julia Beaver, MD	Director, Division of Oncology Products 1 (DOP1)
Amna Ibrahim, MD	Deputy Director, DOP1
Laleh Amiri-Kordestani, MD	Associate Director, DOP1
Lola Fashoyin-Aje, MD, MPH	Acting Clinical Team Lead, DOP1
Jennifer Gao, MD	Clinical Reviewer, DOP1
Tatiana Prowell, MD	Clinical Reviewer, DOP1
Preeti Narayan, MD	Clinical Reviewer, DOP1
Shenghui Tang, PhD	Statistical Team Lead, OB, DBV
Laura Fernandes, PhD	Statistical Reviewer, OB, DBV
Wentao Fu, PhD	Clinical Pharmacologist Team Lead, DCPV
Hisham Qosa, PhD	Clinical Pharmacologist Reviewer, DCPV
Tiffany Ricks, PhD	Acting Nonclinical Team Lead, DHOT
Wei Chen, PhD	Nonclinical Reviewer, DHOT
Christy Cottrell	Chief, Project Management Staff, DOP1
Charlene Wheeler, MSHS	Senior Regulatory Project Manager, DOP1

SPONSOR ATTENDEES

Joseph Posluszny	US Regional Regulatory Head, Regulatory Affairs
Rebecca Mancini	Director, Regulatory Affairs
Amber Ying Zhu	Sr. Associate Director, Regulatory Affairs
Tetiana Taran	Global Program Head
Michelle Miller	Global Program Clinical Head

Celine Wilke	Global Clinical Leader
Mathilde Kaper	Associate Director, Global Program Biostatistics
David Mills	Associate Director, Biostatistics
Lars Blumenstein	Associate Director, Senior Fellow, Clinical Pharmacology
Naveen Babbar	Precision Medicine Leader, Oncology Precision Medicine
Marilyn Fritzemeier	Precision Medicine Director, Oncology Precision Medicine
Jennifer Dacpano-Komansky	Director, Companion Diagnostic Regulatory Affairs
Charlene Ganser	Director, Regulatory CMC
Charu Kochhar	TRD Project Leader
Carolyn Zhu	Postdoctoral Fellow, Regulatory Affairs
Nicola Caria	Medical Director, Clinical Development & Medical Affairs

1.0 BACKGROUND

Novartis requested a type B pre-NDA meeting to discuss a planned NDA submission based upon the results of Study CBYL719C2301 (Study C2301, SOLAR-1) for the following indication:

> *Alpelisib is an α-specific class I phosphatidylinositol-3-kinase (PI3K) inhibitor indicated for the treatment of postmenopausal women and men with hormone receptor-positive, HER2-negative, PIK3CA-mutant advanced breast cancer as detected by a FDA-approved test in combination with fulvestrant after disease progression following an endocrine-based regimen.*

Alpelisib (BYL719) is an investigational oral α-specific class I phosphatidylinositol-3-kinase (PI3K) inhibitor. It has been studied in combination with other agents in several trials with various endocrine therapy backbones for hormone receptor positive, human epidermal growth factor receptor-2 negative (HR+/HER2-) breast cancer, including fulvestrant [Study CBYL719X2101 (Phase 1a) and Study CBYL719C2301 (Phase 3)], letrozole [Study CLEE011X2107 (Phase 1b) and Study CBYL719A2201 (Phase 2)], and fulvestrant or letrozole [Study CBYL719X2402 (BYLIEVE Phase 2)].

Proposed Pivotal Trial

The basis of the NDA submission is Study C2301, a Phase 3 randomized, double-blind, placebo-controlled trial of fulvestrant with or without alpelisib in postmenopausal women and men who have received prior endocrine-based regimens for HR+/HER2-advanced breast cancer. The primary objective of the study was to determine whether fulvestrant plus alpelisib prolongs investigator-assessed progression-free survival (PFS) according to RECIST v 1.1 compared with fulvestrant alone in patients with PIK3CA-mutant advanced HR+/HER2- breast cancer, following disease progression while on or following treatment with an aromatase inhibitor. The PIK3CA mutation status of subjects was centrally assessed using tumor tissue as the basis for study eligibility. Progression-free survival by Blinded Independent Review Committee (BIRC) using a 50% audit was analyzed as a supportive endpoint. Overall survival (OS) in patients with PIK3CA-mutant advanced breast cancer was the key secondary endpoint. Efficacy in patients with PIK3CA non-mutant advanced breast cancer was assessed as a secondary endpoint for proof of concept.

A total of 572 patients were enrolled in SOLAR-1, including 341 in the PIK3CA mutant cohort and 231 in the PIK3CA non-mutant cohort. Patients were randomized 1:1 to receive fulvestrant plus alpelisib 300 mg orally once daily or matched placebo. Within each cohort, randomization was stratified by liver and/or lung metastasis (yes/no) and prior treatment with a CDK4/6 inhibitor (yes/no).

The study met its primary objective at the final PFS analysis. With a 20-month median follow-up as of the June 2018 data cutoff date, alpelisib in combination with fulvestrant demonstrated superiority over fulvestrant monotherapy for the primary endpoint of investigator-assessed PFS in the PIK3CA mutant population. The hazard ratio (HR) was 0.65 (95% CI 0.50, 0.85), p=0.00065. This corresponded to a 5.3-month prolongation of median PFS (11 vs 5.7 months) favoring the alpelisib plus fulvestrant arm. The results of the 50% audit BIRC review were consistent with the investigator assessed PFS results (HR of 0.48 [95% CI: 0.32, 0.71, p=0.00009]) corresponding to a 7.4-month prolongation in median PFS (11.1 vs 3.7 months), in the alpelisib plus fulvestrant arm.

Overall survival results in the PIK3CA mutant cohort were not mature as of the data cutoff date. A total of 92 deaths had been observed, 40 (23.7%) in the alpelisib plus fulvestrant arm and 52 (30.2%) in the control arm), representing a 52% information fraction of the anticipated 178 events for the final OS analysis. The prespecified Lan-DeMets stopping boundary was not crossed. The median OS has not yet been reached for the alpelisib plus fulvestrant arm (95% CI: 28.12, NE) and was 26.9 months (95% CI: 21.91, NE) for the control arm.

The safety population includes both the mutant and non-mutant cohorts. The most common adverse events (AEs) reported in the alpelisib plus fulvestrant arm included hyperglycemia, diarrhea, nausea, anorexia, and rash (all 30% or more). The most common Grade 3-4 AEs in the alpelisib plus fulvestrant arm were similar to the most common AEs: hyperglycemia, rash, and diarrhea. Fewer on- and post-treatment deaths were observed in the alpelisib plus fulvestrant arm compared with the control arm.

Although PIK3CA mutation status for trial eligibility was based upon assessment of tumor tissue samples, plasma ctDNA samples were also collected at baseline from randomized subjects for retrospective determination of plasma PIK3CA mutation status to assess the efficacy of the plasma test (P+ total or P+). Of the 572 subjects randomized to the study, 554 had plasma samples available for testing. Of these 554 subjects, 188 were PIK3CA-mutant and 366 were PIK3CA non-mutant based on plasma ctDNA, whereas 325 were mutant and 229 were non-mutant based on results obtained from tissue specimens. There were 8 discordant cases that were observed for plasma positive samples [i.e., plasma positive/tissue negative (P+T-)] and 145 discordant cases were observed for plasma negative samples (i.e., P-T+). The study results from the retrospective analysis indicate that the PFS was prolonged by 7.2 months in the test arm compared to the placebo arm with an HR of 0.56. Although the HR for P+ is 0.56, the large proportion of P-T+ cases (145 cases) indicates that the plasma assay lacks sensitivity relative to the tissue-based test. The reason for the lack of sensitivity is unknown.

The results in the PFS analysis in PIK3CA subpopulations is shown in the sponsor's table below.

Table 1. Progression-free survival results in PIK3CA subpopulations

		T+ (tissue mutant)	T- (tissue non-mutant)	Total
P+ (plasma mutant)		**P+T+**	**P+T-**	**P+ total**
	No. of subjects	180	8	188
	Hazard ratio	0.57	NE	0.56
	95% CI	0.40, 0.81	NE	0.39, 0.80
	Median PFS (mo)	10.9 vs. 3.7	NE	10.9 vs. 3.7
P- (plasma non-mutant)		**P-T+**	**P-T-**	**P- total**
	No. of subjects	145	221	366
	Hazard ratio	0.82	0.87	0.81
	95% CI	0.54, 1.25	0.59, 1.29	0.61, 1.08
	Median PFS (mo)	11.0 vs. 8.4	7.3 vs. 5.6	8.8 vs. 7.4
Missing plasma	No. of subjects	16	2	18
Total		**T+ total**	**T- total**	
	No. of subjects	341	231	
	Hazard ratio	0.65	0.85	
	95% CI	0.50, 0.85	0.58, 1.25	
	Median PFS (mo)	11.0 vs. 5.7	7.4 vs. 5.6	

Median PFS for alpelisib plus fulvestrant vs. placebo vs fulvestrant

Source: *Copied from meeting packet.*

FDA sent Preliminary Comments to Novartis on October 10, 2018.

2. DISCUSSION

2.1. Questions and Responses

Question 1: Does the Agency agree that the data from the Phase 3 registrational Study C2301 are adequate to substantiate the efficacy and safety of alpelisib, and that the results of this study support filing of the proposed indication.

FDA Response: Yes.

Meeting Discussion: No discussion took place during the meeting.

Question 2: Does the Agency agree to the proposed content of the 120-day Safety Update and timing of the submission in case of priority review?

FDA Response: Yes. In the Safety Update submission (day 90 or 120 for priority or standard review, respectively), please include the updated ADAM datasets and narratives for death, serious TEAEs, and TEAEs resulting in treatment discontinuation.

Meeting Discussion: No discussion took place during the meeting.

Question 3: As alpelisib is a first-in-class product, and the first to treat HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation, Novartis intends to request priority review. The request is justified as alpelisib demonstrates a clinically relevant and statistically

significant improvement in PFS with a manageable safety profile compared to currently available therapy for the treatment of a serious condition. We understand that the decision for the priority review is made at the time of NDA filing. Does the Agency agree with the following justification as a basis for priority review?

FDA Response: We acknowledge your justification; however, as you note, a decision on priority review will be made at the time of filing.

Meeting Discussion: No discussion took place during the meeting.

Question 4: Does the Agency agree that the contents of the NDA as outlined in the proposed electronic Common Technical Document (eCTD) table of contents (TOC) constitute a complete application?

FDA Response: Yes. Please refer to additional clinical pharmacology comments below regarding other general expectations for your NDA submission.

Meeting Discussion: No discussion took place during the meeting.

Question 5: Based on the presence of PIK3CA mutations in Study C2301 (SOLAR-1) subject plasma specimens and demonstration of clinical efficacy with this specimen type, Novartis (b) (4) Does the Agency agree?

FDA Response: We assume that you will be seeking a companion diagnostic claim based upon tissue testing. (b) (4) (b) (4) **You should submit the clinical validation results for the PIK3CA tests along with remaining analytical validation studies under the clinical module of the PMA.**

Meeting Discussion: No discussion took place during the meeting.

ADDITIONAL CLINICAL PHARMACOLOGY COMMENTS

Address the following questions in the Summary of Clinical Pharmacology:

1. **What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.**

2. **What are the exposure-response relationships for efficacy, safety and biomarkers?**

3. **What is the effect of alpelisib on the QT/QTc interval?**

4. **What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?**

5. **What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.**

6. **How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?**

Apply the following advice in preparing the clinical pharmacology sections of the original submission:

1. **Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.**

2. **Provide a final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.**

3. **Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.**

    - **Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.**

    - **Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.**

4. **Submit the following for the population pharmacokinetic analysis reports:**

   - **Standard model diagnostic plots**
   - **Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line**
   - **Model parameter names and units in tables**
   - **Summary of the report describing the clinical application of modeling results**

   Refer to the following pharmacometrics data and model's submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

5. **Submit the following information and data to support the population pharmacokinetic analysis:**

   - **SAS transport files (*.xpt) for all datasets used for model development and validation**
   - **A description of each data item provided in a Define.pdf file. Any concentrations 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 for all major model building steps, (e.g., base structural model, covariates models, final model, and validation model). Submit these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).**

6. **Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at:**

   - **http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for population PK**
   - **http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationships, and**

- **http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for pharmacometric data and model's submission guidelines.**

Novartis Response: Exposure-response analysis for efficacy and safety conducted based on Phase I pooled data and on the SOLAR-1 (Phase III) study data supporting NDA filing will be part of the summary of clinical pharmacology (SCP) appendix instead of standalone study reports. Only the PK/QT and related analysis will be supplied as a standalone report. Does FDA agree?

Meeting Discussion: The FDA agrees with the proposal.

2.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

Topic	Submission	Sponsor Proposed Date	FDA Proposed Date	Agreed Upon Date
1	Module 3 (Quality) 3.2.S.2.1 & 3.2.P.3.1 (Manufacturers)	October 26	October 26	October 26
2	Complete Quality dossier	November 30	November 30	November 30
3	Module 5: SOLAR-1 Datasets Batch 1: SOLAR-1 SDTM and ADaM dataset xpt files to support CSR analyses SOLAR-1 SDRG, ADRG, and ARM documents to support CSR analyses	November 9	November 9	November 9
4	Module 5: SOLAR-1 Datasets Batch 2: SOLAR-1 CRT package plus define.xml files for SDTM and ADaM	November 26	November 26	November 26
5	Module 5: Clinical Study Report for SOLAR-1 (CSR body)	November 9	November 9	November 9
6	Module 5: Complete Clinical Study Report for SOLAR-1	December 6	December 6	December 6
7	Module 2: Summary Documents M2.7 SCE, SCS and SBP without the necessary hyperlinking and appendices	November 26	November 26	November 26
8	Module 2: SCE, SCS and SBP CO and SCP	December 19	December 19	December 19

9	**Module 5: PopPK Report – Phase 1 Phase 3 (The Sponsor to provide a date after internal discussion)**	**December 19**	**November 19**	**November 19**
10	**Module 1 USPI: Entire USPI (not annotated) The Sponsor to provide a date after internal discussion.**	**December 19**	**November 19**	**November 19**
11	**Module 4 (Nonclinical Study Report) + Module 2.6 (Nonclinical summary)**	**November 9**	**November 9**	**November 9**
12	**Module 5: Clinical document-supportive study reports (such as DMPK and validation reports)**	**December 19**	**December 19**	**December 19**
13	**SOLAR-1 CRT package to support CSR, SCE, SCS, and SCP analyses, with description of any changes made since November**	**December 19**	**December 19**	**December 19**
14	**CRT packages for studies X1101 and X2101 (to support SCE, SCS, SCP)**	**December 19**	**December 19**	**December 19**
15	**CRT packages for studies X2107, A2103, A2105, and Z2102 (to support SCP) popPK dataset.**	**November 19**	**November 19**	**November 19**
16	**Full BIMO datasets and OSI package The Sponsor to provide a date after internal discussion.**	**December 19**	**November 9**	**November 9**
17	**Assessment Aid The Sponsor to provide a date after internal discussion.**	**N/A**	**November 26**	**November 26**
18	**CDRH Tissue Module The Sponsor to provide a date after internal discussion with device partner. (Qiagen)**	**January**	**January 2**	**Qiagen will communicate directly with CDRH on October 22, 2018**
19	**Safety Update Report**	**60 days from the final submission date if given priority review**	**60 days from the final submission date**	**FDA request that Novartis submit the ADAM**

			if given priority review	**datasets for the 90/120 day safety update whenever they are ready after database lock to facilitate ongoing review of the NDA submission.**
20	**AOM**	**November**	**December 14**	**December 14**
21	**Final NDA Dossier**	**December 19**	**December 19**	**December 19**

Meeting Discussion: The FDA and the sponsor agreed to conduct the review using the Assessment Aid and the Real Time Oncology Review (RTOR) pilots. The FDA agreed to standing bi-weekly teleconferences with the sponsor, which can be canceled if there no issues requiring discussion. For the CMC section, a decision on standing teleconferences or an extended face to face meeting will be decided once the CMC section is received. If the sponsor has updates to the original submission, they will not replace the original documents, instead they will submit an updated document with tracked changes, summary of changes, and final version. FDA will base their review on the originally submitted documents unless instructed otherwise by the sponsor. The table above represents the agreed upon timeline for submission of components of the application.

- The content of a complete application was discussed. A summary of the discussion and agreements are represented in the table above.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was not held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan, however, it is understood that a REMS and Formal Communication Plan are not needed.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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 or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are

exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020 contain reports of molecularly targeted pediatric cancer investigations. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) 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.

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.				

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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

Attachments used during the meeting are attached below.

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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/

CHARLENE N WHEELER
10/30/2018

IBILOLA A FASHOYIN-AJE
10/30/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119183

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Thomas Esser, PhD
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Esser:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BYL719.

We also refer to the telecon between representatives of your firm and the FDA on May 14, 2015. The purpose of the meeting was to discuss the clinical development program of BYL719 for metastatic breast cancer.

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

If you have any questions, call Charlene Wheeler, Senior Regulatory Project Manager at (301) 796-1141.

Sincerely,

{See appended electronic signature page}

Charlene Wheeler, MSHS
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

{See appended electronic signature page}

Amy McKee, M.D.
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
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: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: May 14, 2015, 1-2pm
Meeting Location: TCON

Application Number: IND 119183
Product Name: BYL719
Indication: Breast Cancer
Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Amy McKee, MD
Meeting Recorder: Charlene Wheeler, MSHS

FDA ATTENDEES

Geoffrey Kim, MD	Director, DOP1
Amna Ibrahim MD	Deputy Director, DOP1
Amy McKee, MD	Clinical Team Leader, DOP1
Tatiana Prowell, MD	Medical Officer, DOP1
Julia Beaver, MD	Medical Officer, DOP1
Todd Palmby, PhD	Pharm/Tox Supervisor, DHOT
Tiffany Ricks, PhD	Pharm/Tox Reviewer, DHOT
Xiao H Chen, PhD	Product Quality Team Leader, OPQ
Jeanne Zirkelbach, PhD	Clinical Pharmacology Reviewer
Shenghui Tang, PhD	Biostatistics Team Leader
Laura Fernandes, PhD	Mathematical Statistician
Soma Ghosh, PhD	Scientific Reviewer, CDRH
Reena Philip, PhD	Director, CDRH
Jiang Liu, PhD	QT-IRT
Christy Cottrell	Chief, Project Management Staff, DOP1
Charlene Wheeler, MSHS	Senior Regulatory Project Manager, DOP1

SPONSOR ATTENDEES

Samit Hirawat, MD	Global Program Head, Oncology Global Development (OGD)
Cristian Massacesi, MD	Global Clinical Program Head, OGD
Nathalie Fretault, MSc	Senior Director, Biostatistics, OGD
Beth DiDomenico, PhD	Senior Director, Drug Regulatory Affairs, OGD
Shanthi Ganeshan, PhD	North America Head, Drug Regulatory Affairs, OGD

Sarah Hersey, PhD	Global Product Diagnostics, Executive Director, Companion Diagnostics, OGD
Mirna DiPano, BS	Global Product Diagnostics, Sr. Associate Director Regulatory Affairs, OGD
Emmanuelle Di Tomaso, PhD	Global Correlative Sciences Lead, OGD
Raoudha Mahjoubi, MD	US Medical Director, Clinical Development and Medical Affairs, OGD
Celine Wilke, MD	Global Clinical Leader, Clinical Development, OGD
Janni Papakrivos, PhD	Global Program Regulatory Manager, OGD
Thomas Esser, PhD	Senior Associate Director, Drug Regulatory Affairs, OGD
Lars Blumenstein	Fellow, Clinical Pharmacology, OGD

1.0 BACKGROUND

BYL719 (alpelisib) is an oral, alpha-specific PIK3CA inhibitor being developed by Novartis for the following proposed indication:

"Alpelisib in combination with fulvestrant is indicated for the treatment of postmenopausal women and men with hormone receptor positive, HER2-negative, (PIK3CA- mutant or (b) (4) advanced breast cancer (b) (4) after disease progression following an endocrine-based regimen."

In 133 evaluable patients with advanced solids tumors who have received alpelisib as a single-agent, a confirmed PR occurred in 7 patients (5%), unconfirmed PR in 8 patients (6%), stable disease in 70 patients (53%), for overall disease control rate of 58%. In breast cancer (n=35), the disease control rate was 63%.

The Sponsor has requested an EOP2 meeting to discuss the design of Study CBYL719C2301 (Solar-1), a randomized double-blind, placebo-controlled trial of fulvestrant at labeled dose/schedule with either alpelisib 300 mg po daily or placebo for the treatment of men and postmenopausal women with hormone receptor positive (HR+), HER2-negative advanced breast cancer and no prior endocrine therapy, or postmenopausal women with HR+, HER2 negative advanced breast cancer who have progressed or relapsed on or after aromatase inhibitor treatment. Patients may have relapsed more than 12 months from completion of (neo) adjuvant endocrine therapy and be treatment naïve in the advanced setting; or relapsed on or within 12 months of completion of (neo) adjuvant endocrine therapy and be treatment naïve in the advanced setting; or relapsed more than 12 months from completion of adjuvant endocrine therapy with documented progression after first-line endocrine therapy for metastatic disease; or have de novo metastatic breast cancer with documented progression after first-line endocrine therapy for metastatic disease.

The primary objective of the trial is to determine whether addition of alpelisib to fulvestrant prolongs progression-free survival (PFS) compared to treatment with placebo plus fulvestrant. Treatment effects will be assessed in two sub-populations: patients with PIK3CA mutated tumors and patients with PIK3CA non-mutated tumors, as defined by central laboratory assessment.

Approximately 820 patients are to be enrolled into the two PIK3CA-defined cohorts (mutant n=340; non-mutant n=480) and randomized 1:1 to receive fulvestrant plus alpelisib or fulvestrant plus placebo. Within each cohort, randomization will be stratified according to the presence of lung and/or liver metastases (yes vs. no) and prior treatment with a CDK inhibitor (yes vs. no).

The primary endpoint of PFS will be assessed by investigator using RECIST v1.1. Blinded independent central review of PFS is planned as supportive evidence. Interim analysis of both PFS and OS are planned, in both the PIK3CA mutant and non-mutant cohorts.

The overall type-1 error (one sided level of significance of alpha=0.025) in testing the primary and the key-secondary endpoints in both cohorts independently will be conserved using a graphical gate-keeping approach and group design strategy. As designed, if the true HR is 0.6 for PFS, corresponding to a 4.9 month improvement in PFS (from 7.4 months to 12.3 months), the study requires 293 PFS events to have 90% power at a one-sided overall 0.5% level of significance to reject the null hypothesis using a log-rank test for a 2-look group sequential design and a gamma spending function to determine the non-binding futility boundary. If the true hazard ratio is 0.67 for OS, corresponding to a 14.8 month improvement in OS (from 30 months to 44.8 months), 178 deaths are needed to have 72% power at a one-sided overall 2% level of significance to reject the null hypothesis using a log-rank test and a 3-look group sequential design.

FDA sent Preliminary Comments to Novartis on May 11, 2015.

2. DISCUSSION

2.1. Clinical

Question 1: Study CBYL719C2301 is a phase 3 randomized trial in postmenopausal women with HR-positive, HER2-negative, advanced breast cancer. Does the agency agree that the study design as outlined in the Briefing Book and the studied patient population will be adequate to support a regulatory filing for the intended indication with regard to:

- dosage and regimen for planned study treatments,
- endpoints,
- stratification factors
- comparator arm (fulvestrant)

FDA Response:
Clarify whether the tablet formulation proposed for Trial CBYL719C2301 is the same as that used in Trial CBYL719X2101 to support the proposed dose in combination with fulvestrant. If the formulations differ, further justification for the current proposed dose in the combination therapy should be provided. The dosage and regimen for the planned treatments are otherwise acceptable.

Consideration of PFS as the primary endpoint for demonstration of efficacy for regulatory approval in metastatic breast cancer is based upon the magnitude of the effect and the risk-

benefit profile. Whether a 5-month improvement in PFS would be considered clinically meaningful in this population will depend on the totality of data and benefit/risk assessment for addition of BYL719 to fulvestrant. While the planned interim analysis for futility is acceptable, we would discourage the planned interim analysis for an efficacy claim. See also response to Question 2.5.

The proposed stratification factors are acceptable. We note that the trial will enroll patients with varying degrees of endocrine sensitivity and caution you that an imbalance in these patients between the two arms may impact the trial results and would be a review issue.

The comparator arm of fulvestrant monotherapy is acceptable, but we caution you that the treatment armamentarium for HR-positive, HER2-negative advanced breast cancer is rapidly changing, and you are likely to encounter feasibility issues in terms of patient accrual with randomization to a fulvestrant alone arm.

Meeting Discussion:
The Sponsor's response regarding the formulations is acceptable.

The Sponsor proposed a new design in which only the *PIK3CA* mutation-positive patient group would be evaluated in the primary endpoint. Fewer wild-type *PIK3CA* patients would be enrolled in a proof-of-concept cohort without any alpha allocation. If the Sponsor goes forward with this plan, FDA recommends enrolling only positive patients with mutation positive *PIK3CA* in this trial and studying patients with wild-type *PIK3CA* in a separate study. FDA also does not object to the original study design in the briefing package.

2.2. CDRH

Question 2: Does the agency agree that the definition and overall plans for development of a companion diagnostic test using a PCR-based approach to define PIK3CA mutant population will support the intended indication, assuming a positive result in the PIK3CA mutant population?

FDA Response:
CDRH considers the proposed test strategy acceptable for patient selection and recommends that you ensure that the assay is fully specified and analytically validated prior to its use in the proposed trial. If *PIK3CA* mutant status is determined to be essential for the safe and effective use of alpelisib, then a companion diagnostic test will be required. If a companion diagnostic is required, then the device and therapeutic will require concurrent approvals.

If the proposed *PIK3CA* PCR mutation assay is different from the 'to-be-marketed' test, then a bridging study will be needed to demonstrate that the 'to-be-marketed' device is safe and effective for its intended use. To the extent possible, the bridging study should retest all samples from the registrational clinical trial with the final "to-be-marketed" device.

Meeting Discussion:
FDA stated that the response from the Sponsor is acceptable.

2.3. Clinical

Question 3: Does the agency agree that the size of the safety database as outlined in the Briefing Book in patients with locally advanced or metastatic breast cancer will be adequate to support a market authorization in the proposed indication?

FDA Response:
Yes.

Meeting Discussion:
No meeting discussion took place.

2.4. Clin Pharm

Question 4: Cardiac safety plans. Based on the information provided in the BB, Novartis intends to collect ECGs at every other cycle during the phase 3 study? Does the Agency agree with this plan?

FDA Response:
We cannot agree based on currently available information. Previous preclinical information and cardiovascular safety in clinical trials are not sufficient to rule out small, clinically relevant increases in the QTc interval (10 ms). A TQT study should be conducted to rule out the risk of small but clinically relevant QTc prolongation if not prevented by tolerability at the therapeutic exposure. If you believe a TQT study is not feasible or small QT prolongation is not concerning for the targeted patients, such justification for not conducting a TQT study should be provided. Because the median Tmax is 2 to 4 hours for the parent drug, ECG/PK collection time points in the phase 3 study should also include 3 hours post-dose (as well as at the Tmax for major metabolites as appropriate).

Meeting Discussion:
FDA acknowledges the Sponsor's clarification regarding the QT assessment plan. FDA suggests that if the Sponsor would prefer earlier input, the plan can be submitted to QT IRT for review prior to the planned clinical pharmacology Type C meeting.

2.5. Statistics

Question 5: Does the Agency agree that the proposed statistical analysis plan (including alpha split used in the graphical gate-keeping approach and group design strategy) described in the Briefing Book are adequate to support a regulatory filing for the proposed indications (b) (4) , assuming a positive result.

FDA Response:
The graphical procedure to control the Type 1 error is acceptable. However, we discourage use of an interim PFS analysis for an efficacy claim.

Consideration of PFS as the primary endpoint for demonstration of efficacy for approval of drug products is based on the magnitude of the effect and the risk-benefit profile of the drug product. An interim PFS analysis may not provide an accurate or reproducible estimate of the treatment effect size due to inadequate follow-up, missing assessments, disagreements between radiological reviewers and/or disagreements between investigator and independent assessments. As documented in literature interim results over estimates the treatment effect.

Meeting Discussion:

No meeting discussion took place.

2.6. Pharm Tox

Question 6: Does the agency agree that the non-clinical plans as outlined in the Briefing Book will adequately support a regulatory filing?

FDA Response:
The completed and planned nonclinical studies with BYL719 appear sufficient to support an NDA submission in the proposed patient population. The final decision regarding the adequacy of the nonclinical data to support approval will be made following review of the NDA submission.

Meeting Discussion:
No meeting discussion took place.

2.7. Clinical

Question 7: Based on the preliminary evidence provided in the Briefing Book, Novartis intends [redacted] (b) (4) Does the Agency agree with the proposal?

FDA Response:
No, we do not believe [redacted] (b) (4)

Meeting Discussion:
The Sponsor will continue to collect data and conduct further analyses, and if additional promising data emerge, the Sponsor will notify the Agency.

Additional Comments:

1. **When feasible, we recommend that you obtain biopsies after progression on aromatase inhibitor or the most recent archival tumor sample available for the analysis of tumor molecular alterations, as the status of these markers may change with tumor progression.**

2. **Consider assessing the status of other molecular alterations that may lead to a reduced sensitivity to PI3K inhibition.**

3. **For the two exploratory endpoints listed in the proposed protocol to assess global health status and pain, analysis in the cohorts of interest is described as "PIK3CA mutant and non-mutant/** (b) (4) [redacted]

Meeting Discussion:
No meeting discussion took place.

3.0
PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

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

Office of Scientific Investigations (OSI) Requests

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

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

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

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

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

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

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

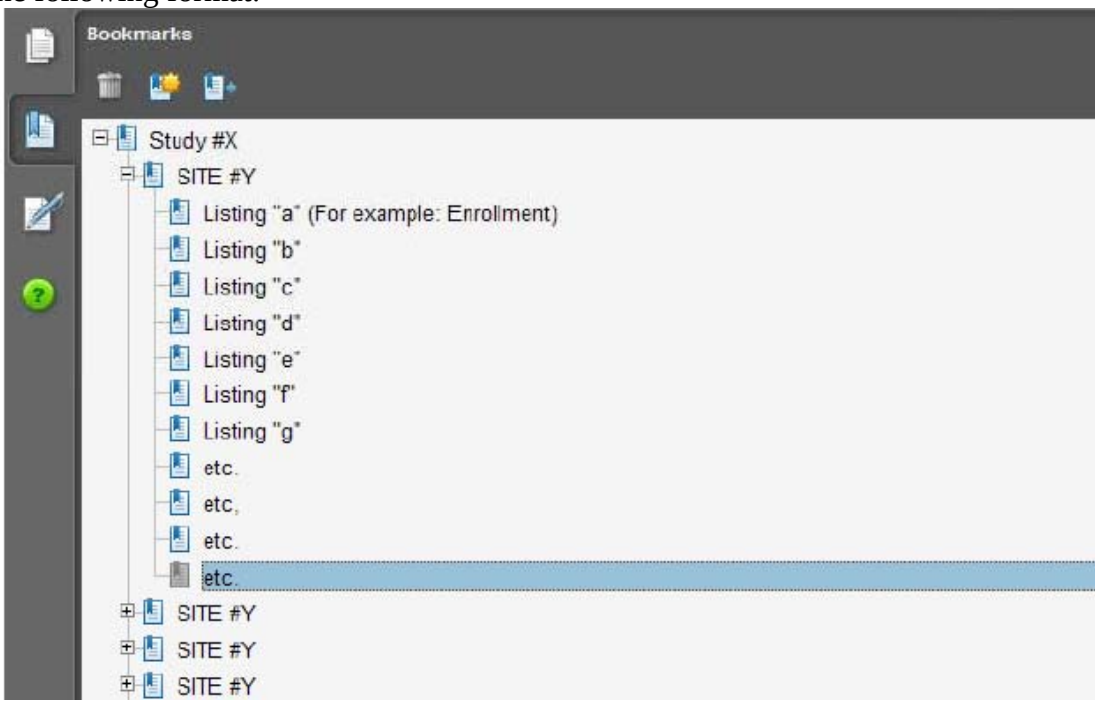
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

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

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

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

Attachment 1

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

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

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

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

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

References:

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

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

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

5.0 ACTION ITEMS

No action items.

6.0 ATTACHMENTS AND HANDOUTS

See below.

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

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

/s/

CHARLENE N WHEELER
05/21/2015

AMY E MCKEE
05/21/2015