CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214958Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 131993

MEETING MINUTES

Bristol-Myers Squibb Company
Attention: Linda Gambone, PhD
Group Director, U.S. Regulatory Lead
Global Regulatory Strategy & Policy
P.O. Box 5326
Mailstop B.2033
Princeton, NJ 08543

Dear Dr. Gambone:[1]

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

We also refer to the telecon between representatives of your firm and the FDA on May 12, 2021. The purpose of the meeting was to discuss the adequacy of your clinical phase 3 data in support of filing and review of the NDA for deucravacitinib.

A copy of the official minutes of the meeting/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 Kimberle Searcy, Regulatory Project Manager, at 240-402-4454.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Sponsor Agenda

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

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	May 12, 2021 9:30 – 10:30 a.m. EST
Meeting Location:	Teleconference
Application Number:	IND 131993
Product Name:	deucravacitinib
Proposed Indication:	For the treatment of adults with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy.
Sponsor Name:	Bristol-Myers Squibb Company
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Kendall A. Marcus, MD
Meeting Recorder:	Kimberle Searcy, MPH

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dentistry (DDD)
Amy Woitach, DO, MS, Clinical Team Leader, DDD
Maryjoy Mejia, MD, Clinical Reviewer, DDD
Soo Hyeon Shin, PharmD, PhD, Clinical Pharmacology Reviewer, Division of Inflammation and Immune Pharmacology
Mohamed Alosh, PhD, Biometrics Team Leader, Division of Biometrics III (DB III)
Marilena Flouri, PhD, Biometrics Reviewer, DB III
CDR Renmeet Grewal, PharmD, MS, RAC, Director, Project Management Staff, Division of Regulatory Operations for Immunology and Inflammation
Kimberle Searcy, MPH, Regulatory Project Manager, Division of Regulatory Operations for Dermatology and Dentistry

SPONSOR ATTENDEES

Matthew Lamb, Pharm D. Regulatory Head of Immunology, Fibrosis & Neuroscience
Linda Gambone, Ph.D., Group Director US Regulatory
Cindy Rubin, MD, Program Regulatory Lead
Mathias Hukkelhoven, Ph.D., SVP Regulatory
Jennifer Dudinak, Head of Regulatory, Strategy & Policy
Dorothy Waddleton, Executive Director, Regulatory Immunology, Fibrosis & Neuroscience
Elizabeth Colston, MD, Ph.D., Clinical Development Lead, Dermatology
Marla Hochfeld, MD, Head of Clinical Development Immunology, Fibrosis & Neuroscience
Rosemary Petric, Ph.D., Head of Clinical Research Scientists

Ian Catlett, Ph.D., Scientific Director, Clinical Biomarkers CV, fibrosis, immunology
Subhashis Banerjee, MD, VP and Disease Area Head, Dermatology and Rheumatology
Mary Beth Harler, MD, SVP Immunology and Fibrosis Development
Allison Smitten, MD, ScD, Medical Safety Assessment, Worldwide Patient Safety
Daniel Seekins, MD, VP, Medical Safety Assessment, Immunology, CV, Fibrosis & Neuroscience
John Throup PhD, Program Development Lead, Dermatology
Sudeep Kundu Ph.D., Executive Director, Global Biometric Sciences
Tao Wang, Ph.D., Director, Biostatistics
Dominic Labriola, Ph.D., VP Global Biometric Sciences
Anjaneya Chimalakonda Ph.D. Director, Clinical Pharmacology and Pharmacometrics
Urvi Aras, Ph.D., Sr. Director, Clinical Pharmacology and Pharmacometrics
Brian Todd, Associate Director, Clinical Trial Risk Assessment Lead
Regina Regan, Associate Director, Therapeutic Area Quality
Greg Vico, Sr. Director, Therapeutic Area Quality

1.0 BACKGROUND

Purpose of Meeting:
The purpose of this meeting is to discuss the adequacy of your clinical phase 3 data in support of filing and review of the NDA for deucravacitinib.

CORONAVIRUS – 19 (COVID 19) CLINICAL TRIAL GUIDANCE

During the COVID-19 public health emergency, ensuring the safety of study participants is paramount. Sponsors should consider each circumstance, focus on the potential impact on the safety of study participants, and modify study conduct accordingly. It is critical that study participants are kept informed of changes to the study and monitoring plans that could impact them, and that the Agency is appropriately informed of these changes. Refer to the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency*. We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm [2]

2.0 DISCUSSION

2.1. Regulatory

No regulatory questions were submitted for this meeting.

2.2 Chemistry, Manufacturing, and Controls (CMC)

No CMC questions were submitted for this meeting.

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

2.3 Nonclinical

No nonclinical questions were submitted for this meeting.

2.4 Clinical Pharmacology

Question 2:
Does the FDA agree that the clinical pharmacology package, including the plan for population PK (PPK) and exposure-response (E-R) analyses, is adequate to support the NDA filing and review in the proposed indication: deucravacitinib for the treatment of moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy?

FDA Response to Question 2:
Your clinical pharmacology package appears adequate to support the NDA filling in general. We recommend that you address drug interaction potential of metabolites in your NDA submission. Refer to the guidance for industry *In Vitro Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* for details. https://www.fda.gov/media/134582/download

Meeting Discussion:
No discussion occurred at the meeting.

2.5 Clinical/Biostatistics

The development program for deucravacitinib (BMS-986165) for the treatment of adults with moderate to severe plaque psoriasis includes the following studies:

Phase 2:

- IM011-011: a completed multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 2 study evaluated the efficacy and safety of multiple doses of deucravacitinib [3 mg daily (QD), 3 mg every other day (QOD), 3 mg twice a day (BID), 6 mg BID, 12 mg QD] in 267 adults with moderate to severe plaque psoriasis.

The dose 6 mg QD for the phase 3 studies were based on PK modeling.

Phase 3:

- IM011-046: an ongoing 52-week, multi-center, randomized, double-blind, placebo- and active-controlled study to evaluate the efficacy and safety of deucravacitinib in 666 subjects with moderate-to-severe plaque psoriasis (defined as PASI ≥ 12, sPGA score ≥ 3, and BSA involvement ≥ 10%) who were randomized in a 2:1:1 ratio to one of the following 3 treatment groups: deucravacitinib, apremilast, or placebo.

- IM011-047: an ongoing 52-week, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled study with a randomized withdrawal and retreatment phase to evaluate the safety and efficacy of deucravacitinib in 1020 subjects with moderate-to-severe plaque psoriasis who were randomized in a 2:1:1 ratio to one of the following 3 treatment groups: deucravacitinib, apremilast, or placebo.

- IM011-075: an ongoing open-label, multicenter, phase 3 extension study to evaluate the long-term safety of deucravacitinib in subjects with moderate to severe plaque psoriasis who were enrolled in a prior relevant phase 3 study, including but not limited to IM011-046 and IM011-047, as well as IM0110065 and IM011-066 (the latter two are regional studies in Asian and Japanese subjects respectively).

Question 1A:
Does the FDA agree that the efficacy data from pivotal studies IM011046 and IM011047 are adequate to support the NDA filing and review for the proposed indication: deucravacitinib for the treatment of moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy?

FDA Response to Question 1A:
Your proposal to submit results from pivotal studies IM011046 and IM011047 to support the NDA filing and review for the proposed indication appears reasonable. We note that the previous comments provided in the preliminary comments (dated November 13, 2020) for the previously requested Pre-NDA meeting still apply.

The Agency originally noted that efficacy be established based on data for subjects with complete in-person visits and requested that you submit your SAP for comments. However, you did not submit your SAP and the Agency did not have the chance to provide additional feedback. In the current briefing package, you noted that none of the subjects missed Week 16 visit. You also stated subjects who missed efficacy assessments due to COVID-19 were to be (b) (4) We note that our previous comment was intended for establishing efficacy, yet we are exploring other approaches which may be more reasonable for handling missing visits due to COVID-19 for assessing efficacy during the treatment period as well as during the maintenance period. Therefore, we recommend that you consider alternative approaches for handling the missing data due to COVID-19, other than the current approach of (b) (4) (b) (4).

We also have the following additional comments:

- On August 13, 2019 you notified the Agency regarding the discontinuation of Site 0092 by Dr. Melody Stone based on findings of non-compliance with ICH Guidelines for Good Clinical Practice. You further noted that two subjects were

enrolled at this site; however, the subjects elected to discontinue from the study. Clarify how these subjects were handled in the primary analysis of both primary and key secondary endpoints.

- You noted that the "other" reasons for discontinuation reported in your disposition tables include subject's request to discontinue for a variety of personal or work-related reasons, subject's request to discontinue due to perceived lack of efficacy or dissatisfaction with study treatment, and reasons related to COVID-19. We recommend separating out the reasons related to COVID-19 rather than including them in the "other" category.

- We reiterate our comment conveyed in advice letters dated October 29, 2018 and December 6, 2019 that the key secondary endpoint for change in PSSD score may not be clinically meaningful to appear in labeling. In addition, we reiterate that establishing efficacy claims against apremilast based on endpoints and/or timepoints other than the ones used to establish efficacy of apremilast depends on clinical relevance along with control for multiplicity and will be a review issue.

- You stated that "although not statistically significant, a numerical improvement was observed for PGA-F 0/1 (fingernail); these data will be provided in the NDA as a pooled summary to increase the sample size." We reiterate our comment provided in the preliminary comments dated November 13, 2020 that analyses based on pooled efficacy data are considered exploratory. Establishing an efficacy claim would be based on efficacy data from the individual phase 3 trials along with a replication of study findings.

Meeting Discussion:
The Agency agreed with the sponsor's proposal to conduct sensitivity analyses using NRI and multiple imputation to assess the impact of missed visits due to COVID-19 will be included in the submission for key secondary endpoints at Weeks 24 and 52. The Agency further recommended the use of a model based imputation when conducting multiple imputations to account for subject responses at the visits prior to missing visits due to COVID-19.

Question 1B:
Does the FDA agree that the safety data from pivotal studies IM011046 and IM011047 are adequate to support the NDA filing and review for the proposed indication: deucravacitinib for the treatment of moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy?

FDA Response to Question 1B:
You propose that the safety database include all available data from two phase 3 studies (IM011046 and IM011047; referred to as the Controlled Safety Pool) and the LTE Study IM011075 (referred to as the phase 3 Safety Pool). The Controlled Safety

Pool will include 1364 subjects who were treated with deucravacitinib (969 patient-years), of which 1257 subjects were treated with deucravacitinib for 16 weeks and 503 subjects were treated with deucravacitinib for 52 weeks. Your proposed safety database will not provide sufficient long-term exposure to support a determination of the benefit/risk for the use your novel product in the systemic treatment of plaque psoriasis.

Additionally, on January 29, 2021 you submitted correspondence to inform the Agency of a Potential Serious Breach related to study treatment assignment during the Randomized Withdrawal and Maintenance period in the clinical study IM011-047. The incident concerns an integrated response technology (IRT) error causing subjects to not be changed back to active treatment (deucravacitinib) after experiencing a protocol defined relapse [at least a 50% loss of the Week 24 Psoriasis Area and Severity Index (PASI) percent improvement from baseline]. You reported that the number of subjects impacted is 10% (N=106) of the 1020 randomized subjects who had a relapse and should have been switched back to active treatment. We consider that the ability to characterize the safety profile of deucravacitinib has been impacted.

Regarding to the Integrated Summary of Safety (ISS), we refer you to the preliminary comments dated November 13, 2020. In addition, we recommend that for Summary 2 (Week 0 -24) of the Controlled Safety Pool, the deucravacitinib arm includes only subjects treated with deucravacitinib for 24 weeks (i.e., exclude subjects who switched from placebo to deucravacitinib at Week 16) to allow a cleaner comparison to apremilast. For the same reason, we recommend that you include in the deucravacitinib/apremilast arms subjects treated with deucravacitinib/ apremilast for 52 weeks for Summary 3 (Week 0-52). We remind you of our preliminary comment dated November 13, 2020 that whether Summary 3 will inform the risk benefit assessment will be a review issue.

We further recommend that you consider a between-arm summary measure (e.g., difference in EAIRs between the treatment arms) for comparisons between deucravacitinib and placebo and between deucravacitinib and apremilast for the controlled phase 3 pool, when such comparison(s) is appropriate. In particular, we recommend that the tables present the following in each treatment arm:

A. The number of subjects
B. The number of subjects with the adverse event
C. The percent of subjects with the event
D. The number of exposure years
E. The point estimate of the exposure-adjusted incidence rate, along with the corresponding 95% confidence interval
F. The point estimate of the between-group summary measure (e.g., difference in exposure-adjusted incidence rates), along with the corresponding 95% confidence interval

The SAP for the ISS should specify an appropriate statistical method to construct the 95% CIs.

Meeting Discussion:
The Agency highlighted the need for an adequate safety database at the time of NDA submission in order that a risk benefit assessment for deucravacitinib can be made with class risks associated with JAK inhibitors. They acknowledged this product's novel mechanism of action but pointed out that claims of relative safety compared to other JAK inhibitors remains undemonstrated. As a result, the Agency advised the sponsor to submit a safety database that includes 1100 subjects exposed to deucravacitinib for at least one year with the original NDA submission (see sponsor's response appended to the meeting minutes).

The sponsor stated that in addition to their proposed primary safety evaluation, they will also include supplemental summaries as part of Summary 2 (0-24 wk) and Summary 3 (0-52 wk) including subjects who did not switch therapy during the relevant period. The Agency noted that such proposal appears reasonable.

The sponsor also stated that they will include the requested between-arm summaries for all AEs within the Controlled Safety Pool for the following summaries: deucravacitinib vs placebo (0-16 weeks) and deucravacitinib vs apremilast (0-16 weeks, 0-24 weeks, and 0-52 weeks). The sponsor proposed to conduct these analyses for those populations for which there are no treatment switches involved, in addition to the population originally proposed.

Post-Meeting Comment:
The Agency advises the sponsor to submit the safety database at the time of submission of the NDA.

Question 3:
Does the FDA agree with the BMS plan for Risk Management?

FDA Response to Question 3:
You anticipate that labeling will provide adequate risk mitigation in the post-marketing setting and do not plan to include a Risk Evaluation and Mitigation Strategy (REMS) in the initial application. You consider that post-marketing "pharmacovigilance activities" will be sufficient to inform any changes to the benefit-risk profile. The basis for your proposed plan is that you have not identified serious safety issues in your two pivotal studies. Based on the limited, high-level information that you have presented in the meeting package, your plan appears reasonable. However, an assessment on risk and plans for mitigation will be a review issue.

Meeting Discussion:
No discussion occurred at the meeting.

Question 4:
Does the FDA agree with the BMS plan for characterizing findings, management, and impact from Quality Management assessments within the planned NDA submission?

FDA Response to Question 4:
Your proposal to provide information on deviations from Good Clinical Practice (GCP) and the serious data breach as well as remediations and an assessment of impact in data integrity appears reasonable. It is difficult to make judgement about the impact of such deviation, including data breaching, from the GCP in the absence of detailed information related to such deviations. We request that you provide us with details including whether specific deviations occurred on a study level (i.e. impacting all centers) versus deviations which are specific to certain centers, an explanation of how did you find that about the deviations and the action you took to fix such deviations, including dates. The potential impact of these deviations on patient safety, data quality and study integrity will be a review issue. Refer to the response in Question 1B.

Meeting Discussion:
No discussion occurred at the meeting.

3.0 ADMINISTRATIVE COMMENTS

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.[3] 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.[4]

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 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,

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[3] 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.

[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

[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

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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[7]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[8]

4.0 SPONSOR AGENDA

- Question 1a
- Question 1b

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

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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/

KENDALL A MARCUS
06/10/2021 04:37:01 PM

IND 131993

MEETING PRELIMINARY COMMENTS

Bristol-Myers Squibb Company
Attention: Linda Gambone, PhD
Group Director, U.S. Regulatory Lead
P.O. Box 5326
Mailstop B.2033
Princeton, NJ 08543

Dear Dr. Gambone:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for deucravacitinib tablet, 6 mg.

We also refer to your September 8, 2020 correspondence requesting a meeting to discuss the structure and organization of your proposed NDA submission.

Our preliminary responses to your meeting questions are enclosed.

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

If you have any questions, call me at 301 796-4224.

Sincerely,

{See appended electronic signature page}

Barbara Gould, MBAHCM
Chief, Project Management Staff
Division of Regulatory Operations for
Dermatology and Dentistry
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: November 16, 2020, 1:30 p.m.— 2:30 p.m. EDT
Meeting Location: Teleconference

Application Number: IND 131993
Product Name: deucravacitinib tablet, 6 mg

Proposed Indication: For the treatment of adult patients with moderate to severe psoriasis

Sponsor Name: Bristol-Myers Squibb Company
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetics Act

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for November 16, 2020, 1:30 p.m.— 2:30 p.m. EDT between Bristol-Myers Squibb Company and the Division of Dermatology and Dentistry. 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

The purpose of this meeting is to discuss the structure and organization of your proposed NDA submission.

Regulatory History:

We have had the following meetings/teleconferences with you:

- November 26, 2018 — Written Responses
- March 7, 2018 — Type B End-of-Phase 2

We have sent the following correspondences:

- July 8, 2020 — Advice
- December 6, 2019 — Advice
- April 2, 2019 — Advice
- December 3, 2018 — Agreed Initial Pediatric Study Plan Agreement
- October 29, 2018 — Advice
- August 30, 2018 — Advice
- August 8, 2018 — Initial Pediatric Study Plan Written Responses
- February 7, 2018 — Advice
- July 26, 2017 — Special Protocol Agreement
- December 8, 2016 — Study May Proceed

Coronavirus 19 (COVID-19) Clinical Trial Guidance

During the COVID-19 pandemic, ensuring the safety of trial participants is paramount. Sponsors should consider each circumstance, focus on the potential impact on the safety of trial participants, and modify study conduct accordingly. It is critical that trial participants are kept informed of changes to the study and monitoring plans that could impact them, and that the Agency is appropriately informed of these changes. Refer to the FDA guidance on *Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency*. We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

2.0 DISCUSSION

2.1. Regulatory

No regulatory questions were submitted for this meeting.

2.2. Chemistry, Manufacturing and Controls (CMC)

No CMC questions were submitted for this meeting.

2.3. Nonclinical

No nonclinical questions were submitted for this meeting.

2.4. Clinical Pharmacology

Question 1:

Does the Agency agree with the overall content of the Clinical Pharmacology and Biopharmaceutical sections?

FDA Response to Question 1:
The proposed Clinical Pharmacology and Biopharmaceutical sections appear reasonable at this time; however, if you have used formulations other than the to-be-marketed formulation in the clinical pharmacology studies, and you plan to use the information from such studies to inform labeling, then you would need to provide data to support establishment of a bridge between the different formulations used in your clinical pharmacology studies and the to-be-marketed formulation. The adequacy of the clinical pharmacology data will be a review issue at the time of your NDA submission.

Question 2:
Does the Agency agree with the proposed data submission plan for Clinical Pharmacology and Pharmacometrics?

FDA Response to Question 2:
Yes, the proposed data submission plan for Clinical Pharmacology and Pharmacometrics appears reasonable.

2.5. Clinical/Biostatistics

Question 3:
Does the Agency agree with the proposed pooling strategy for the integration of efficacy data in the Summary of Clinical Efficacy (SCE; Module 2.7.3) and Integrated Summary of Efficacy (ISE; Module 5.3.5.3)?

FDA Response to Question 3:
You plan to provide an Integrated summary of Efficacy (ISE) by pooling the two pivotal Phase 3 clinical trials IM011046 and IM0011047. Your proposed pooling strategy for the integration of efficacy data in the Summary of Clinical Efficacy and Integrated Summary of Efficacy appears reasonable. Note that the ISE should include discussions regarding the strength of evidence across all trials, including discussion of any difference in outcomes across trials. We also note that the objective of the ISE is to support the analysis results obtained from the individual trials and not to establish a new efficacy claim based on pooled data. Therefore, analyses based on pooled efficacy data are considered exploratory. Establishing an efficacy claim would be based on efficacy data from the individual Phase 3 trials along with a replication of study findings.

Question 4:
Does the Agency agree with the proposed format and content for the SCE and ISE?

FDA Response to Question 4:
Your proposed format and content appear reasonable.

Question 5:
Does the Agency agree with the proposed pooling strategy for the integration of safety data in the Summary of Clinical Safety (SCS; Module 2.7.4) and Integrated Summary of Safety (ISS; Module 5.3.5.3)?

FDA Response to Question 5:
You propose to pool the safety data from the two pivotal clinical trials (IM011046 and IM011047), as your primary safety pool, along with the LTE study (IM011075) as your secondary supportive safety analysis. Your primary safety pooling strategy appears reasonable. However, for your proposed Summary 3 for the period of Week 0 to 52, you plan to (b) (4) (b) (4) We note that your proposed approach (b) (4) may lead to overestimation of the safety signal (b) (4) Whether Summary 3 will inform the risk benefit assessment will be a review issue.

Provide easy access to all safety narratives for serious adverse events, serious events that lead to discontinuation, and adverse events of interest. Additional supportive safety data are provided from supportive studies.

Question 6:
Does the Agency agree with the proposed format and content for the SCS and ISS?

FDA Response to Question 6:
You propose to provide your SCS content in Module 2.7.4. Your proposal is reasonable.

Question 7:
Does the Agency agree with the proposed plan for inclusion of Subject Narratives and Case Report Forms (CRFs) in support of the planned NDA submission?

FDA Response to Question 7:
Clinical Safety Narratives and CSRs should be easy to access and hyperlinked from Module 2.7.4 where your Safety Content is described. Your proposal appear to be reasonable.

Question 8:
Does the Agency agree with the content and scope of the 120-day safety update report?

FDA Response to Question 8:
Identify how many subjects will have 52-week safety data from your pivotal Phase 3 clinical trials (primary safety pool) at submission of the NDA and how many subjects in your primary safety pool and the LTE study (IM011075) will be included in the 120-day safety update report.

Question 9:
Does the Agency agree with the proposed data submission plan for pivotal and supportive clinical studies?

FDA Response to Question 9:
Your proposal to submit SDTM and ADaM formatted datasets for the Psoriasis trials is acceptable. Sensitivity analyses for the handling of missing data in the Phase 3 trials include a multiple imputation method and a tipping point analysis. You should submit the SAS code used to implement the proposed multiple imputation methods as well as the SAS code used to analyze the imputed datasets. Also, submit the SAS code to implement the tipping point analysis.

For the analysis datasets, we have the following general comments:

a. Each analysis dataset should include treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables, including the center variables (i.e., original and analysis), needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies. Further, assign a unique ID to the original site (center) to permit analysis across the Phase 3 trials.

b. The analysis dataset documentation (Define.xml) should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables.

In addition to the electronic datasets, you should submit study protocols including the statistical analysis plan (SAP), all protocol and SAP amendments (with dates), generated treatment assignment lists, and the actual treatment allocations (along with the date of enrollment).

Additional Comments for the protocol and SAP amendments submitted on October 8, 2020:

c. The protocol/SAP should pre-specify the primary estimand of interest along with methods for handling intercurrent events (e.g., study discontinuation). In addition, you should provide a justification that this estimand and the statistical methods utilized to estimate it are appropriate. Refer to ICH E9 (R1) for defining and explaining your estimand, available at https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf

Additional Comments related to Statistical Impacts Due to COVID-19:

d. We acknowledge the difficulty in handling subjects with missed assessment visits due to the COVID-19 pandemic. The impact of missed visit assessments will be driven by the proportion of subjects who missed their visits due to the COVID-19 pandemic as well as by the treatment duration prior to missing the final live visit. For these factors it is difficult to provide detailed comments about handling subjects with missed in person visit due to the COVID-19; however, we note that efficacy should be established based on data for subjects with complete in-person visits. Following establishing a treatment effect, sensitivity analyses can be conducted to investigate the impact of missed visits on the overall efficacy assessment. We acknowledge that you specified sensitivity analyses for the endpoints affected by COVID-19 using the last observation carried forward (LOCF); however, as the scientific justification for using LOCF is generally weak, you should provide an adequate rationale for using LOCF or propose more scientifically sound methods with different assumptions than the LOCF to assess the impact of various methods. You should submit your plan for handling missed visits due to COVID-19 for Agency review.

e. Furthermore, we recommend that you monitor subject enrollment and disposition without unblinding the data to decide whether you may need to increase enrollment to compensate for subjects who cannot continue in the trial due to COVID-19 disruptions. You should submit your proposal for increase in trial enrollment, if any, to the Agency for review. Also, you should receive IRB approval for modifying the protocol to increase the enrollment of the trials.

We note that, your datasets for safety and efficacy should include data for all randomized subjects including those who missed visits due to Covid-19, along with all necessary variables related to COVID-19 information, such as dummy variables for subjects who discontinued or missed visits/data due to reasons related to COVID-19 and subjects who had dosing interruptions related to COVID-19 to allow sensitivity analyses.

Question 10:

Does the Agency agree with the approach BMS is taking in providing Bioresearch Monitoring (BIMO) summary level clinical site data for FDA data integrity review and inspection for the two pivotal Phase 3 studies (IM011047 and IM011046)?

FDA Response to Question 10:

Yes, we agree with your approach. In addition to the guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, also see *CDER's Bioresearch Monitoring Technical Conformance* for more information on FDA specifications, recommendations, and general considerations for preparing and submitting Clinical Study-Level information, Subject-Level Data Line Listings by Clinical

Site, and a Summary-Level Clinical Site Dataset that are used for planning of BIMO inspections. It's available at: https://www.fda.gov/media/85061/download.

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our September 28, 2020 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

Information on the Program is available at FDA.gov.[1]

PREA REQUIREMENTS

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

[1] 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*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of 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.

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- 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.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical 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*

373 *Specifications*.[6]
374
375
376

[6] https://www.fda.gov/media/85061/download

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BARBARA J GOULD
11/13/2020 08:27:56 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 131993

MEETING MINUTES

Bristol-Myers Squibb Company
Attention: Cindy J. Rubin, MD
Group Director, Global Regulatory Lead-Immunology
P.O. Box 4000
Princeton, NJ 08543

Dear Dr. Rubin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BMS-986165.

We also refer to the telecon between representatives of your firm and the FDA on March 7, 2018. The purpose of the meeting was to discuss the development program for BMS-986165 in the treatment of adults with moderate to severe plaque psoriasis.

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 Barbara Gould, Chief, Project Management Staff at (301) 796-4224.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Product
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
BMS Response to Meeting Preliminary Comments

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:	March 07, 2018 at 11:00 AM EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	IND 131993
Product Name:	BMS-986165
Proposed Indication:	Treatment of adults with moderate to severe plaque psoriasis
Sponsor Name:	Bristol-Myers Squibb Company
Meeting Chair:	Kendall Marcus, MD
Meeting Recorder:	Barbara Gould

FDA ATTENDEES
Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
David Kettl, MD, FAAP, Clinical Team Leader, DDDP
Gary Chiang, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Cindy (Xinguang) Li, Pharmacology Reviewer, DDDP
Mohamed Alosh, PhD, Biometrics Team Leader, Division of Biometrics III
Marilena Flouri, PhD, Biometrics Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Clinical Pharmacology (DPC) III
Yanhui Lu, PhD, Clinical Pharmacology Reviewer, DCP III
Jiang Liu, PhD, Pharmacometrics Reviewer,
Selena Daniels, PharmD, MS, Team Leader, Clinical Outcomes Assessment (COA)
Yasmin Choudhry, MD, Reviewer, COA
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP

SPONSOR ATTENDEES
Subhashis Banerjee, MD - Clinical Program Lead
Tai-Tsang Chen, PhD - Head, Biostatistics
Ihab Girgis, PhD - TA Head, Clinical Pharmacology & Pharmacometrics

Mary Beth Harler, MD - Head, Innovative Medicines Development
Sudeep Kundu, PhD - TA Head, Biostatistics
Jacob Lesniak, PhD - Principal Scientist, Toxicology, Drug Safety Evaluation
Prathibha Rao, PhD, MBA - Global Regulatory Team Leader, (US Liaison)
Cindy J. Rubin, MD - Global Regulatory Team Leader
John Throup, PhD - Development Lead
Anthony Waclawski, PhD - Head, Regulatory & Pharmaceutical Sciences

1.0 BACKGROUND

The purpose of this meeting is to discuss the development program for BMS-986165 in the treatment of adults with moderate to severe plaque psoriasis.

Regulatory Correspondence History

We have sent the following correspondences:

- 11/21/2017 Meeting Request Denied
- 07/26/2017 Special Protocol Agreement – SPA -1 & -2 Carcinogenicity
- 12/08/2016 Study May Proceed

2.0 DISCUSSION

2.1. Nonclinical

Question 1a:
Does the Agency agree that the outlined nonclinical safety pharmacology and toxicology programs are sufficient to support further development and application for the approval of BMS-986165 for an indication of adults with moderate to severe plaque psoriasis?

FDA Response to Question 1a:
Yes, your nonclinical package outlined in Table 3 on pages 23 & 24 and your ongoing/planned nonclinical toxicology studies detailed in Section 2.4 on page 25 of your briefing package appears reasonable to support initiation of Phase 3 clinical studies and an NDA submission. We note that you indicated in Table 3 that the rat fertility study was a preliminary study. Submit the full study report for a GLP completed rat fertility study for review prior to initiation of Phase 3 clinical studies. The determination of the nonclinical data adequacy will be made after the review of the submitted full study reports under the IND/NDA.

Question 1b:
Based on the data and proposed studies presented thus far, does FDA have any comments which need further discussion?

FDA Response to Question 1b:
We do not have additional comments at this time.

2.2. Clinical Pharmacology

Question 2:
Does the Agency agree that the proposed clinical pharmacology program is sufficient to support an application for the approval of BMS-986165 for an indication of adults with moderate to severe plaque psoriasis?

FDA Response to Question 2:
The proposed clinical pharmacology program seems reasonable; however, whether additional studies are needed will be determined after we fully review your study reports and the adequacy of data from your program at the time of NDA submission.

To help you design studies in specific populations, we refer you to:

- Draft guidance for industry: *Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010).*

- Guidance for industry: *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (May 2003).*

2.3. Clinical /Biostatistics

Introductory Comments:
You have completed a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, Phase 2 study (IM011011), where you investigated the following doses:

- BMS-986165, 3 mg every other day (QOD; n=42)
- BMS-986165, 3 mg once daily (QD; n=42)
- BMS-986165, 3 mg twice daily (BID; n=42)
- BMS-986165, 6 mg BID (n=42)
- BMS-986165, 12 mg QD (n=42)

The response rates based on PASI 75 showed a dose-trend, and the 3 highest doses of BMS-986165 (3 mg BID, 6 mg BID and 12 mg QD) showed similar responses. Similarly, the 3 highest doses showed similar response rates based on PASI 90, while response rates based on sPGA 0/1 were higher in the 3 mg BID and 12 mg QD doses compared to the rest of the doses.

You are proposing to conduct two placebo- and active comparator-controlled Phase 3 trials in subject with moderate-to-severe psoriasis (IM011-046/047). Though not obligatory, you have chosen apremilast as a comparator in the Phase 3 development program. Based on modeling, you selected BMS-986165 6 mg QD dose for the Phase 3 trials.

The two Phase 3 trials are 52-week, multicenter, randomized, double-blind, placebo- and active comparator- controlled trials; however, Trial IM011-147 additionally has a randomized

withdrawal and maintenance period. The proposed co-primary endpoints in the two Phase 3 trials are: (i) the proportion of subjects who achieve a 75% improvement in Psoriasis Area and Severity Index from baseline (PASI 75) to Week 16, and (ii) the proportion of subjects who achieve a static Physician's Global Assessment (sPGA) score of 0 (clear) or 1 (minimal) at Week 16.

We have the following general comments regarding your Phase 3 trials:

- While you listed two co-primary endpoints, it should be noted that the division gives priority to success based on the sPGA for judging efficacy, and consequently, testing for such endpoint should be given priority.

- You listed many secondary endpoints, some evaluated at more than one time point. Some of the endpoints may not be clinically meaningful. Although you may evaluate many secondary endpoints for your product, you are encouraged to have a limited number of secondary endpoints intended for labeling. Endpoints not included in the multiplicity strategy will be considered exploratory.
- It should be noted that you powered your trials using "expected" response rates for BMS-986165 6 mg QD, as this dose was not investigated in your Phase 2 study (IM011011). You may be taking the risk of under-powering your Phase 3 trials based on assumed response rates.

- You plan to stratify randomization by several factors, including biologic use, body weight and geographic region, which may complicate the conduct of the trials and the analysis. Stratification should be limited to factors expected to impact efficacy. The Agency is interested in investigating heterogeneity in treatment effect across centers/regions.

- You did not specify in the protocol synopses the primary efficacy analysis population. The primary efficacy analysis population should be the intent-to-treat (ITT) population, defined as all randomized subjects who dispensed drug medication. In addition to the ITT population, we recommend defining a per-protocol (PP) population in the protocol as a supportive analysis population. The key protocol deviations that define the PP population should be pre-specified in the protocols.

- You propose to analyze continuous efficacy endpoints (i.e. change and percent change from baseline in PASI, and change from baseline in (b) (4) PSSD) using (b) (4) It should be noted that the results from an approach (b) (4) might not be clinically meaningful (b) (4) As efficacy is to be established at Week 16, your analysis should be based specifically on the Week 16 data; however, modeling approaches using all time-points may be used as supportive/sensitivity analyses.

- In Trial IM011-047, you plan to re-randomize subjects at Week 24, who originally were randomized to BMS-986165 6 mg QD and achieved PASI 75 response, to two

maintenance arms (BMS-986165 and placebo). We recommend that re-randomization be based on the sPGA responders instead of PASI 75 responders; see also our comment about giving priority to sPGA when judging efficacy.

- In Trial IM011-047, you defined relapse as a ≥ 50% increase in the PASI score compared with that at Week 24. If a subject experience a relapse at any visit during this period, the subject will be treated with BMS-986165 6 mg QD until the end of the treatment period (Week 52). We recommend the definition of relapse to be based on the sPGA instead of PASI; see also our comment about giving priority to sPGA when judging efficacy.

- We recommend that you collect surveillance pharmacokinetic (PK) samples in the proposed Phase 3 trials to gather additional information on the systemic exposure of your drug product in the to-be-marketed formulation and dose as well as to conduct population PK analysis if needed.

Question 3a:
Does the Agency agree that the overall design of the proposed Phase 3 studies, IM011-046 and IM011-047, is adequate to support approval of BMS-986165 at a dose of 6 mg QD for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy?

FDA Response to Question 3a:
See Introductory Comments under Section 2.3 Clinical/Biostatistics. The proposed dosing regimen of 6 mg daily is reasonable for evaluation in Phase 3 based on the results from your Phase 2 trial.

Question 3b:
Is the anticipated overall clinical safety data package adequate to support the assessment of the safety and benefit-risk profile in an application for approval of BMS-986165 in adults with moderate to severe plaque psoriasis?

FDA Response to Question 3b:
See Introductory Comments under Section 2.3 Clinical/Biostatistics regarding estimating your response rate for the 6 mg QD dose, which was not studied during your Phase 2 dose-ranging study. Your estimated subjects for each of the Phase 3 clinical trials would provide a combined safety database of 1139 subjects exposed to at least one dose of BMS-986165, with 977 exposed to 16 weeks and up to 468 exposed for 52 weeks. In addition to the proposed and completed early phase clinical studies, your safety database should be adequate to support your application. The adequacy of your safety database will be a review issue based on the performance of your product.

Your high-level approach to adjudicating adverse events, including assessments for depression and suicide, appears acceptable.

Meeting Discussion:
Regarding (b) (4)*, we recommend that you submit information to support it content validity and psychometric performance in this context of use for FDA review. In addition, the Agency recommends use of CCSRS, PHQ-8, and* (b) (4) *in your clinical trials.*

Question 4a:
Are the two Phase 3 studies adequately designed to support a claim of superiority of BMS-986165 over apremilast consistent with the regulatory expectations of the Agency?

FDA Response to Question 4a:
Comparative efficacy information for systemic psoriasis products could be a useful addition to product labeling. Replication of findings would be required.

You may establish superiority of BMS-986165 over apremilast based on the endpoints used to establish efficacy of apremilast (i.e., sPGA score 0/1 and PASI 75 at Week 16). Establishing superiority over apremilast based on other endpoints and/or time points depends on clinical relevance along with control for multiplicity.

Question 4b:
Assuming the data are supportive, does the Agency agree that such results, (b) (4) , will be described in the USPI?

FDA Response to Question 4b:
If adequate statistical rigor is demonstrated, comparative data for your proposed product vs. apremilast is appropriate for Section 14 of labeling. The final content of labeling will be determined by review of the data submitted in your NDA. See FDA Response in Question 4a.

Question 5:
Does the Agency agree that the Phase 3 studies are adequately designed to seek the labeling of:

a. maintenance of effects up to Week 52;
b. durability of response after cessation of therapy; and
c. (b) (4)

FDA Response to Question 5:
See Introductory Comments under Section 2.3 Clinical/Biostatistics. There is a distinction between a comparative efficacy claim against an approved product and comparative information during maintenance. For establishing a comparative efficacy claim, the same endpoints as well as timepoints should be used as for the approved product. For describing maintenance of response, the trial should pre-specify criteria for loss of response using the same endpoints as for defining success and pre-specify a targeted response by a certain timepoint(s). Maintenance information can be pre-specified as secondary endpoints.

For Trial IM011-047, you specified several key secondary endpoints at Week 52 to evaluate maintenance of efficacy. It should be noted that formal statistical testing against subjects re-

randomized to placebo for the maintenance is not meaningful. Note that descriptive analyses/statistics for maintenance, such as the proportion of subjects who maintain their response over the maintenance period and time to relapse (for an appropriate definition of relapse) after treatment withdrawal, are meaningful and can be presented in the label.

Meeting Discussion:
The sponsor inquired about using PASI 75 responders for randomization for the evalution of maintenance and durability of response. The sponsor agreed to provide data for the maintenance period will be descriptive and no formal testing will be done.

The Agency noted that our preference is for maintenance should be based on success of the PGA, as such an endpoint, is the recommended endpoint for establishing efficacy. While randomization can be carried at for subject success in the PGA, the sponsor can randomize subjects who achieve success on PASI 75 but are not successful on PGA. If they desire to meet the regulatory requirements of other Agencies.

Question 6:
Does the Agency agree that demonstration of efficacy in (b) (4) (b) (4) (b) (4)?

FDA Response to Question 6:
(b) (4)

(b) (4)

Meeting Discussion:

(b) (4)

Question 7:

BMS is planning to use both the Psoriasis Symptom and Sign Diary (PSSD) symptom score and the PSSD sign score as key secondary endpoints to support clinical efficacy. Does the Agency agree that if statistically significant improvements in the PSSD symptom score and/or the PSSD sign score are observed, the results could be included in the Clinical Studies section of the USPI as providing valuable information for patients and prescribers?

FDA Response to Question 7:

The results from PSSD should demonstrate both statistically significance and clinically meaningfulness to patients.

While we agree that achieving a score of 0 on the PSSD total score, symptom score, and sign score are clinically meaningful endpoints, it is unclear how the PSSD will be scored in the registration trials. The briefing package indicates that scores will be transformed on a 0-100 scale, however, the proposed endpoints appear to be based on the raw scores (i.e., endpoints are based among subjects who have a score of at least 1 at baseline). We recommend that the sponsor use raw scores to enhance data interpretability.

Inclusion of PRO data in the product label will depend on the adequacy of submitted data and the strength and limitations of the instrument within the given context of use, and the design and conduct of the trial.

Additional comments:

(b) (4)

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

2. (b) (4)

3. When appropriate and feasible, we recommend electronic data capture using a device with a reminder or alarm function as this tends to facilitate operation, minimize the extent of missing data. We recommend electronic data capture for daily diaries using a device with reminder or alarm functions when feasible, as this tends to minimize missing data and allows for the collection of other important information (e.g., timestamps for data input). You may refer to the FDA Guidance for Industry on electronic source data.[1]

4. While not a requirement, we recommend you perform usability testing of the selected devices with patient cognitive interviews to assess device functionality, questionnaire comprehension, and ease of use in the patient population if it has not be completed already. This would minimize the likelihood of having poor quality data due to patients' misunderstanding or incomplete understanding of how to use the device. We also recommend you implement a back-up plan (e.g., web- or paper-based) in case of any malfunctions with the electronic devices, prior to using the devices in your Phase 3 trials.

Question 8:
Does the Agency agree with BMS proposals for the methods for handling of missing data in the statistical analyses of the primary and secondary endpoints?

FDA Response to Question 8:
For binary efficacy endpoints, you propose using the non-responder imputation (NRI) method for the handling of missing data. For continuous efficacy endpoints, you propose using (b) (4) for the handling of missing data. It should be noted that the approach for handling missing data should be consistent for all endpoints otherwise it might be difficult to interpret study findings.

In addition, you stated that "several other analyses will be presented to assess the sensitivity of the above analyses for handling missing data". It should be noted that the protocols should include at least two sensitivity analyses for handling missing data that use different

[1] Guidance for Industry: Electronic Source Data in Clinical Investigations (http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm328691.pdf)

assumptions from the primary imputation method to ensure the results are not driven by the method of imputation.

Question 9:
Does the Agency agree that the results of the key secondary endpoints can be described in the Clinical Studies section of the USPI, if statistically significant superiority of BMS-986165 6mg QD is demonstrated for these key secondary endpoints with an adequate control of the Type I error rate?

FDA Response to Question 9:
See Clinical Introductory comments. The final content of labeling will be determined by review of the data submitted in your NDA.

Question 10a:
Does the Agency agree with the BMS proposal to study only a single dose (6 mg QD) in each of the two Phase 3 studies to fully evaluate the benefit-risk profile of BMS-986165 in support of the indication for adults with moderate-to-severe plaque psoriasis?

FDA Response to Question 10a:
Your choice of 6 mg QD dosing in the proposed two Phase 3 pivotal trials appears reasonably safe.

Question 10b:
If not, does the Agency have any comments with regard to (b) (4)
(b) (4)

FDA Response to Question 10b:
(b) (4)

Question 11a:
Does the Agency have any comments or concerns regarding the (b) (4)?

FDA Response to Question 11a:
You are proposing to (b) (4)
(b) (4)

Details of your statistical treatment for this subset should be provided for review.

Meeting Discussion:
The Agency stated that the safety database should support (b) (4).

Question 11b:
If the data are supportive, could these data be potentially considered for labeling in the Dosage and Administration and the Clinical Studies sections of the label?

FDA Response to Question 11b:
The final content of labeling will be determined by review of the data submitted in your NDA.

Question 12a:
Does the Agency have any comments regarding the Sponsor's plan to have a separate unblinded internal team to prepare data for NDA filing as described above while the study teams remain blinded through completion of the clinical trials at Week 52?

FDA Response to Question 12a:
It would be difficult to provide detailed comments about having a separate unblinded team to analyze the data while the study is ongoing. However, for maintaining the integrity of the trial you should ensure that data are blinded throughout the study.

Question 12b:
In the event that the 16-week data are strongly supportive of superiority to apremilast in terms of efficacy, and that sufficient safety have been collected to support the initiation of a submission with FDA, would the Agency be open to a discussion of the results and the potential for an expedited filing should the data be supportive of this approach?

FDA Response to Question 12b:
"Expedited filing" is not included in Agency programs for expedited drug development. For more information on available programs, see the Agency guidance, *Expedited Programs for Serious Conditions – Drugs and Biologics.*

3.0 ADMINISTRATIVE COMMENTS

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.

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.pdf), 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 start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or 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 start 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.

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

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

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

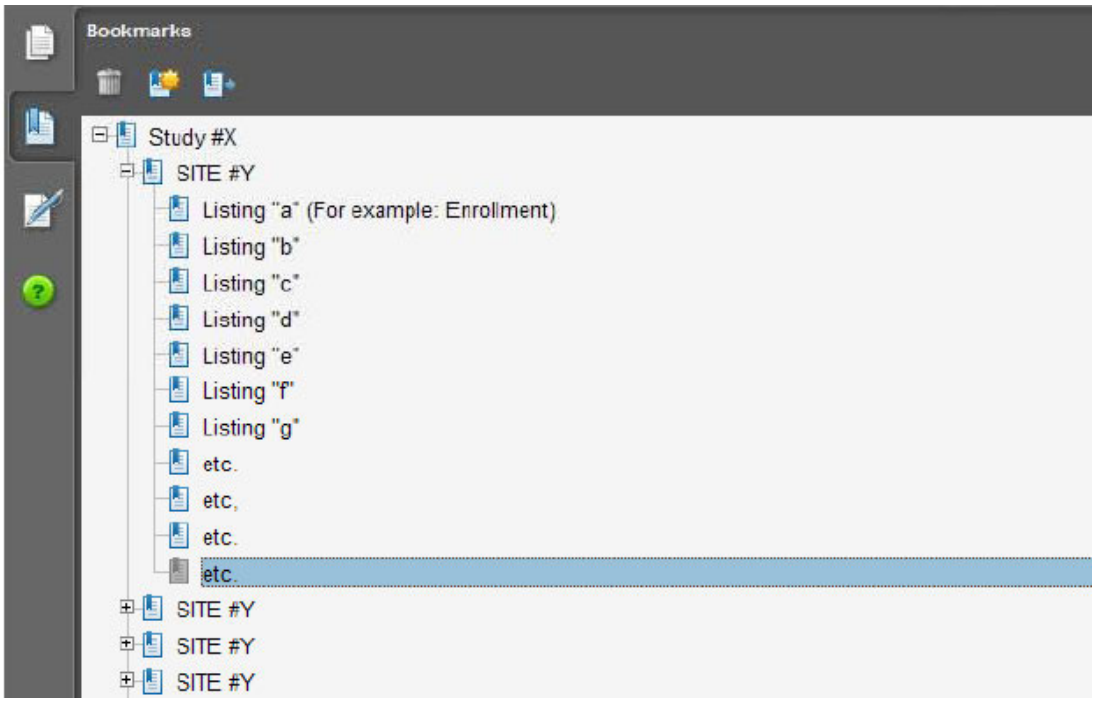
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, 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[2]	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.

[2] Please see the OSI Pre-NDA/NDA Request document for a full description of requested data files

References:

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

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

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

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.

4.0 ATTACHMENTS AND HANDOUTS

On Tuesday, March 06, 2018, BMS provided their response to the meeting preliminary comments.

32 Pages 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/

KENDALL A MARCUS
06/21/2018