CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213217Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 125326

MEETING MINUTES

BeiGene, Ltd.
c/o BeiGene USA, Inc.
Attention: Julie Boisvert, BSc.
Director, Regulatory Affairs
2929 Campus Drive, Suite 300
San Mateo, CA 94403

Dear Ms. Boisvert:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BGB-3111.

We also refer to the meeting between representatives of your firm and the FDA on May 30, 2019. The purpose of the meeting was to discuss the topline results from the pivotal studies and to seek comments and agreement from the Agency on the timing of the new drug application (NDA) for mantle cell lymphoma.

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 Rachel McMullen, Senior Regulatory Project Manager at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Lead
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: May 30, 2019; 3:00-4:00PM (ET)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: IND 125326
Product Name: BGB-3111; zanubrutinib
Indication: Mantle Cell Lymphoma (MCL)
Sponsor Name: BeiGene Ltd.
Regulatory Pathway: 505(b)(1)

Meeting Chair: R. Angelo de Claro, MD
Meeting Recorder: Rachel McMullen, MPH, MHA

FDA ATTENDEES

SPONSOR ATTENDEES

1.0 BACKGROUND

BeiGene Ltd. is developing BGB-3111, an oral Bruton's tyrosine kinase (BTK) inhibitor for the treatment of various B-cell malignancies. The proposed indication is for the treatment of mantle cell lymphoma who have received at least one prior therapy. The proposed proprietary name is zanubrutinib. The drug was granted orphan drug designation by the FDA for the treatment of (b) (4) mantle cell lymphoma (MCL) on June 23, 2016 (#16-5274), respectively. Fast-track designation was granted on July 19, 2018. The Phase 1 study BGB-3111-AU-003 in B-cell malignancies was initiated in Australia, New Zealand, South Korea, USA, Italy and the UK. A Phase 3 study of BGB-3111 in WM (BGB-3111-302) was subsequently activated.

Interactions with the Agency include:

- End-of-Phase 1 meeting on May 12, 2016 to present data from the ongoing Phase 1 Study BGB-3111-AU-003 and obtain input on registrational pathways and study designs for the MCL, (b) (4).

- Type C meeting on April 5, 2017 to discuss the developmental plan for BGB-3111 in (b) (4) which the sponsor elected to cancel upon review of the Agency's preliminary responses dated March 29, 2017.
- Type C teleconference on June 27, 2017 on the design of study (b) (4)
- Type C meeting written responses provided on November 17, 2017 regarding the clinical pharmacology plan in (b) (4)
- Type C (CMC specific meeting) on December 7, 2017 regarding starting materials, drug substance and drug product specifications, manufacturing sites, and stability data package.
- (b) (4)
- Type C meeting on August 31, 2018 regarding NDA plans for zanubrutinib in MCL patients.
- Type C WRO meeting on October 30, 2018 regarding the content and format of the proposed marketing application with written responses provided to the Sponsor.
- (b) (4)
- Type B teleconference on February 7, 2019 to discuss the study design for a pivotal and confirmatory Phase 3 Study (BGB-3111-306) in Mantle Cell Lymphoma.
- Type B meeting WRO meeting on April 17, 2019 to discuss the content and format of their proposed new drug application to pursue accelerated approval of zanubrutinib for patients with Mantle Cell Lymphoma (MCL).
- (b) (4)

On March 20, 2019, BeiGene requested a Type B pre-NDA meeting to discuss the topline results from the pivotal studies and to seek comments and agreement from the Agency on the timing of the new drug application (NDA) for mantle cell lymphoma.

FDA sent preliminary comments to BeiGene on May 23, 2019.

2. DISCUSSION

Question 1**:** *Does the Agency agree that the efficacy and overall safety profile are adequate to support the filing of a new drug application for zanubrutinib in MCL?*

FDA Response: Data from studies BGB-3111-206 and BGB-3111-AU-003 appear adequate for the assessment of the benefit-risk for zanubrutinib for the treatment of patients with mantle cell lymphoma who have failed at least one prior therapy. The Agency will conduct our own independent analyses of the datasets to confirm the efficacy and safety findings. A decision on filing and subsequent review of the NDA will be made during the filing review.

Please ensure compliance with Study Data Standards and the latest version of the STUDY DATA TECHNICAL CONFORMANCE GUIDE: Technical Specifications Document
https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

Please provide the following in the submission:

a. Executable, clearly commented, non-macro programs in ASCII format used to create tables and figures for primary and key secondary efficacy analyses and any additional information included in Section 14 CLINICAL STUDIES of the Prescribing Information, if applicable. Ensure that programs call only data submitted to the Agency and can be easily used to reproduce the results in the CSR. Ensure that variables used in the programs for generating results in the CSR are described clearly in the define file.
b. To facilitate the analysis, please include code in programs that explicitly converts submitted .xpt files into the data format used by programs.
c. A clear index with descriptions of the programs
d. Annotations for each figure and table in the CSR with a list of datasets and variables, as well as a link to the program used to generate results.

DISCUSSION: There was no discussion.

Question 2: *Does the Agency agree with the stability data proposal that BeiGene will submit 9-month stability data from primary stability batches at the time of NDA submission and may submit 12-month data during the review cycle?*

FDA Response: We agree with your proposal to submit 9 months of primary stability data at the time of initial NDA submission and follow up with the 12-month update approximately 2 months after NDA filing in August 2019. Be advised that any data provided 30 days after the initial submission may not be reviewed depending on internal goal dates and available resources. Expiration dating period for the proposed drug product will be assigned based on the quantity and quality of data available at the time of review.

DISCUSSION: There was no discussion.

Question 3: *Based on the preliminary safety profile of zanubrutinib, we believe that the potential risks will be adequately addressed through labeling and that a Risk Evaluation*

and Mitigation Strategy (REMS) will not be necessary. Does the Agency concur with this approach?

FDA Response: At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

DISCUSSION: There was no discussion.

ADDITIONAL CLINICAL COMMENTS:

1. For more sensitive and informative safety analyses, selective grouping of PTs is necessary beyond that used for adverse events of special interest (AESIs). For example, reporting of "sepsis" should include preferred terms of "septic shock" and specific types of sepsis. For the safety analyses, FDA therefore uses a combination of grouped and ungrouped PTs. In addition, when reporting frequencies of AEs by body system (SOC), AEs that involve more than one body system should be consolidated and reported under the most commonly involved or most appropriate body system, in order to avoid underreporting. Include PTs involving more than one body system / SOC under the one most appropriate body system.

2. Include a list of preferred terms that were included for each grouped terms.

3. Include an assessment of any discrepancies of the incidence of AEs between trials 3111-206 and 3111-AU-003 (i.e. contusion (37% vs 1%), hemorrhage (54% vs 25%).

DISCUSSION: The Sponsor plans to include a list of terms for grouped AEs in the NDA and will include a location in the reviewer's guide. The Sponsor plans to address additional comment #3 in the summary of clinical safety. These proposals are acceptable to the Agency.

The Agency recommended pre-submission of manufacturing sites and BIMO information to the NDA prior to full NDA submission.

The Agency and the Sponsor reached agreement on the definition of a complete application.

There will be no formal late component submissions.

The need for a REMS will be determined during review of the marketing application.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. **The Agency and the Sponsor reached agreement on the definition of a complete application.**

- 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 held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan. **The need for a REMS will be determined during review of the marketing application.**

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

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 any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined 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. See link to list of relevant molecular targets below. 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 include plans 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 the latest version of the molecular target list, please refer to FDA.gov.[1]

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*.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

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[1] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm5 44641.htm

[2] 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[3] and Pregnancy and Lactation Labeling Final Rule[4] 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.

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3 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm08 4159.htm

4 http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm09 3307.htm

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[5]

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.[6]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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

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*.[7]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[8]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- AssessmentAid[9]

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7 https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRe quirements/UCM332468.pdf

8 https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm61292 7.htm

9 https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm61292 3.htm

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

NA

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting summary.

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/

ROMEO A DE CLARO
05/31/2019 10:55:28 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 125326

MEETING MINUTES

BeiGene, Ltd.
C/o BeiGene USA, Inc.
Attention: Julie Boisvert, BSc.
Director, Regulatory Affairs
2929 Campus Drive, Suite 300
San Mateo, CA 94403

Dear Ms. Boisvert:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BGB-3111.

We also refer to the teleconference between representatives of your firm and the FDA on February 7, 2019. The purpose of the meeting was to discuss the study design for a pivotal and confirmatory Phase 3 Study (BGB-3111-306) in Mantle Cell Lymphoma (MCL).

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

If you have any questions, call Rachel McMullen, Senior Regulatory Project Manager at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
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:	B
Meeting Category:	Discuss the study design for a pivotal and confirmatory Phase 3 Study (BGB-3111-306) in Mantle Cell Lymphoma (MCL).
Meeting Date and Time:	February 7, 2019; 3:00-4:00PM (ET)
Meeting Location:	Teleconference
Application Number:	IND 125326
Product Name:	BGB-3111
Indication:	Mantle Cell Lymphoma (MCL)
Sponsor/Applicant Name:	BeiGene Ltd.
Meeting Chair:	Angelo de Claro, MD
Meeting Recorder:	Rachel McMullen, MPH, MHA

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Ann Farrell, MD, Director
Angelo de Claro, MD, Clinical Team Leader
Margret Merino, MD, Medical Officer
Rachel McMullen, MPH, MHA, Senior Regulatory Project Manager

Office of Biostatistics/Division of Biometrics V
Jingjing Ye, PhD, Statistical Team Leader
Alexei Ionan, PhD, Statistical Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Ruby Leong, Pharm D, Clinical Pharmacology Team Leader
Lili Pan, Pharm D, Clinical Pharmacology

SPONSOR ATTENDEES

BeiGene:
Jane Huang, MD, Chief Medical Officer, Hematology
Eric Hedrick, MD, Chief Advisor, Executive Team
Rebecca Elstrom, MD, Senior Medical Director, Clinical Development
William Novotny, MD, Vice President, Clinical Development
Sunhee Kwon Ro, PhD, Senior Director, Biostatistics
Shibao Feng, PhD, Director, Biostatistics

Rachel Wei, PhD, Director, Biostatistics
Ying Ou, PhD, Senior Director, Clinical Pharmacology
Julie Boisvert, B.Sc., Senior Director, Regulatory Affairs
Sylvia Guirguis, B.Sc., Senior Manager, Regulatory Affairs

1.0 BACKGROUND

BeiGene Ltd. is developing BGB-3111, an oral Bruton's tyrosine kinase (BTK) inhibitor for the treatment of various B-cell malignancies. The proposed indication is for the treatment of (b) (4) The proposed proprietary name is zanubrutinib. The drug was granted orphan drug designation by the FDA for the treatment of (b) (4) mantle cell lymphoma (MCL) on (b) (4) June 23, 2016 (#16-5274), respectively. Fast-track designation was granted on July 19, 2018. The Phase 1 study BGB-3111-AU-003 in B-cell malignancies was initiated in Australia, New Zealand, South Korea, USA, Italy and the UK. A Phase 3 study of BGB-3111 in WM (BGB-3111-302) was subsequently activated.

Interactions with the Agency include:

- End-of-Phase 1 meeting on 12 May 2016 to present data from the ongoing Phase 1
- Study BGB-3111-AU-003 and obtain input on registrational pathways and study designs for the MCL, (b) (4).
- Type C meeting on 05 April 2017 to discuss the developmental plan for BGB-3111 in (b) (4) which the sponsor elected to cancel upon review of the Agency's preliminary responses dated 29 March 2017.
- Type C teleconference on 27 June 2017 on the design of study (b) (4)
- Type C meeting written responses provided on 17 November 2017 regarding the clinical pharmacology plan in (b) (4)
- Type C (CMC specific meeting) on 07 December 2017 regarding starting materials, drug substance and drug product specifications, manufacturing sites, and stability data package.
- (b) (4)
- Type C meeting on August 31, 2018 regarding NDA plans for zanubrutinib in MCL patients.
- Type C WRO meeting on October 30, 2018regarding the content and format of the proposed marketing application with written responses provide to the Sponsor
- (b) (4)

On, December 17, 2018, BeiGene requested a Type B meeting to discuss the study design for a pivotal and confirmatory Phase 3 Study (BGB-3111-306) in Mantle Cell Lymphoma.

FDA sent Preliminary Comments to BeiGene on February 4, 2019.

2. DISCUSSION

Preamble: The Agency has identified major concerns with your proposed confirmatory trial for MCL. The following key issues should be addressed:

1. [redacted] (b) (4) For a single confirmatory trial designed to verify clinical benefit in mantle cell lymphoma, your primary hypothesis testing should be for superiority.

2. Data to address potential drug-drug interactions and dose modification recommendations for zanubrutinib in the protocol are insufficient. Refer to additional clinical pharmacology comments below.

DISCUSSION:
As part of the Breakthrough Designation, the Sponsor provided an overview of the submission plan for the initial NDA in June 2019 and pre-NDA meeting in March 2019. The Agency acknowledged the proposed submission plan.

DISCUSSION:
The Agency provided clarification on the objections with use of [redacted] (b) (4) **due to the following reasons:**

[redacted] (b) (4)

Hence, the Agency recommended superiority primary analysis for PFS.

The Sponsor inquired regarding execution of different SAPs for FDA and with other regulatory agencies. The Agency has no objections with this approach provided that the FDA SAP should reflect a primary efficacy analysis of superiority for PFS. The Sponsor should also take measures to ensure integrity of the trial if SAPs that differ between regulatory authorities are implemented.

Regarding safety claims, the trial would need to be adequately designed for the clinical and statistical evaluation of safety endpoints in the appropriate population, including assurance that the safety endpoints are consistently implemented across all sites. In general, the Agency recommends double blind, controlled trials with central adjudication of endpoints to support comparative safety claims.

The additional data you have provided appears to support your proposed dosing recommendations of zanubrutinib with co-administration of strong and moderate CYP3A4 inhibitors and inducers for Study 306. Further FDA comments may be conveyed following review of your submitted DDI study report and PBPK report.

Question 1: *Does the Agency agree with the study design for the confirmatory Phase 3 study of zanubrutinib in patients with previously untreated MCL? Selected aspects of the study include:*

a. *Eligibility requirement of a confirmed diagnosis of MCL based on the World Health Organization (WHO) 2008 classification of tumors for hematopoietic and lymphoid tissue*

FDA RESPONSE: No. We recommend using the updated WHO 2016 revision to the classification of lymphoid neoplasms as this incorporates recently identified subclasses of mantle cell lymphoma that may have a more indolent clinical course. Your protocol should specify that the diagnosis of mantle cell lymphoma should include cyclin D1 and/or t(11,14) testing.

b. *The patient population comprised of patients with previously untreated MCL age ≥ 65 years for whom stem cell transplantation is not planned.*

FDA RESPONSE: We do not object to your proposed patient population of previously untreated MCL ≥ 65 years. With regards to patients for whom stem cell transplantation is not planned; you should collect data on the specific reasons that patients were not considered eligible for stem cell transplantation and this information should be recorded in the CRF.

DISCUSSION: The Sponsor acknowledged the Agency's concerns and will address this in the protocol.

c. *The proposed stratification factors: MCL International Prognostic Index (MIPI) score (low vs intermediate or high), age (≥ 70 years versus < 70 years) and geographic region (North America/Europe vs Asia Pacific).*

FDA RESPONSE: Your proposed stratification factors are reasonable.

d. *The control therapy of bendamustine plus rituximab.*

FDA RESPONSE: Your proposed control arm of bendamustine plus rituximab would be reasonable for a trial designed to demonstrate superiority in your proposed population of patients with previously untreated MCL who are not candidates for SCT.

With regards to maintenance rituximab therapy, we note that the data suggesting that maintenance rituximab may not benefit patients after bendamustine therapy (MAINTAIN trial) is preliminary (PFS HR 0.64 [95% CI 0.36, 1.14]) and based on 47 PFS events in 120 patients randomized to rituximab maintenance or observation. We also note that all patients on this trial received 2 additional doses of rituximab after BR therapy. The small number of events and small sample size does not allow for conclusive statements on lack of benefit of rituximab maintenance in patients who receive BR as firstline treatment for MCL.

In your proposed trial, patients receiving BR will receive only 6 cycles of rituximab and there may be concerns that this arm will underperform compared to accepted therapy. You should also consider how patients who may receive maintenance rituximab due to investigator preference or emerging data will be handled in the analysis plan.

DISCUSSION: The Sponsor acknowledged the Agency's concerns and will address this in the protocol.

e. The assessment of response according to the Lugano Classification for Non-Hodgkin Lymphoma (NHL) (Cheson et al, 2014)

FDA RESPONSE: Your plan to utilize IRC assessed response based on the Lugano Classification of NHL is reasonable. You should specify that FDG-PET will be required on all patients, as this is a key component of the Lugano criteria.

Question 2: *Does the Agency agree with the following statistical considerations for this Phase 3 study?*

a. The primary endpoint of progression-free survival, determined by independent central review using the Lugano Classification for NHL.

FDA RESPONSE: While we agree that PFS is an acceptable endpoint for a randomized trial in mantle cell lymphoma, we do not agree with your planned (b) (4) (see preamble).

b. The secondary endpoints of progression-free survival determined by investigator assessment using the Lugano Classification for NHL, overall response rate, duration of response, overall survival, rate of CR or complete metabolic response, time to response and patient-reported outcomes.

FDA RESPONSE: We do not object to your proposed secondary endpoints of ORR, CR rate and OS as secondary endpoints. All other endpoints would be considered exploratory, including PRO endpoints.

In the absence of a statistically significant result for the primary analysis of the primary endpoint, results based on secondary endpoints, subgroups, or further analyses of the primary endpoint cannot result in (either singly or in combination) an efficacy claim. Given a statistically significant result for the primary analysis of the primary endpoint, significant secondary endpoints, after proper adjustment for multiplicity to guarantee a study-wise one-sided 0.025 type I error rate, may be included in the label. Please clearly specify key primary and key secondary efficacy endpoints for which claims may be included in the labeling and how adjustments will be made for multiplicity to guarantee a study-wise one-sided 0.025 type I error rate.

Your disease assessment of schedule of every 12 weeks for 24 months, then every 24 weeks for an additional 24 months is acceptable. (b) (4)

[redacted] (b) (4) For patients who have not experienced an IRC-assessed PFS event at 48 months, disease assessment should continue every 24 weeks.

DISCUSSION: The Agency explained that assessment frequency for PFS should be no longer than every 6 months in order to reliably estimate median PFS for therapies with expected long PFS duration.

c. *The primary hypothesis testing to demonstrate* [redacted] (b) (4)

FDA Response: No. See Preamble.

[redacted] (b) (4)

FDA Response: No. Discussion of [redacted] (b) (4) is premature due to lack of agreement on primary and secondary hypothesis testing plans. See Preamble.

Question 3: *If the primary endpoint of the study is met and the benefit:risk ratio of zanubrutinib plus rituximab is favorable, does the Agency agree that this Phase 3 study (BGB-3111-306) would be sufficient to:*

a. *Serve as the confirmatory trial for the above-referenced accelerated approval of zanubrutinib in relapsed or refractory MCL (regular approval) and*

FDA Response to Question 3a: It is premature to discuss this given that we do not have an agreement on the statistical analysis plan for the primary endpoint.

[redacted] (b) (4)

Additional Clinical Pharmacology Comments

1. Include the following recommendations in the protocol for Study BGB-3111-306:
   a. Provide data to support zanubrutinib dose adjustment for concomitant use of moderate CYP3A inducers/inhibitors. In the absence of data, remove dose adjustment recommendations for concomitant use of moderate CYP3A inducers/inhibitors.

b. Revise the inclusion criterion with regards to hepatic function to total bilirubin ≤ 1.5 × ULN given that bendamustine should not be used in patients with moderate or severe hepatic impairment.
c. Consider collecting additional PK sampling timepoints of zanubrutinib for population PK and exposure-response analyses.

2. During clinical development of zanubrutinib, conduct a clinical study or utilize a physiologically-based pharmacokinetic modeling approach to evaluate the effect of a moderate CYP3A inhibitor and inducer on the pharmacokinetics of zanubrutinib and to determine appropriate dosing recommendations.

3.0 OTHER IMPORTANT MEETING

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.

SUBMISSION FORMAT REQUIREMENTS

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

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

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

A copy of the sponsor's presentation materials is attached for reference.

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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/

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02/08/2019 02:06:24 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 125326

MEETING MINUTES

BeiGene USA, Inc.
Attention: Julie Boisvert
Director, Regulatory Affairs
2929 Campus Drive, Suite 300
San Mateo, California 94403

Dear Ms. Boisvert:

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

We also refer to the meeting between representatives of your firm and the FDA on October 25, 2018. The purpose of the meeting was to:

- Seek concurrence on the proposed Drug Product Stability Package
- Gain agreement on the Dissolution Method
- Seek concurrence on the bridging approach to demonstrate comparability between the clinical batches used in the pivotal registrational study and the intended commercial drug product.

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

If you have any questions, call Rabiya Haider, Pharm.D., at (240) 402-6153.

Sincerely,

{See appended electronic signature page}

Anamitro Banerjee, Ph.D.
Branch Chief, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: October 25, 2018; 11:00 AM- 12:00 PM EST
Meeting Location: White Oak Building 22, Conference Room: 1417

Application Number: 125326
Product Name: Zanubrutinib
Indication: (b) (4)

Sponsor/Applicant Name: BeiGene USA, Inc.

Meeting Chair: Anamitro Banerjee, PhD
Meeting Recorder: Rabiya Haider, PharmD

FDA ATTENDEES

Office of Pharmaceutical Quality Office of New Drug Products (ONDP)
Anamitro Banerjee, Ph.D., Branch Chief
Sherita McLamore, Ph.D., Acting Quality Assessment Lead (Drug Product)
Xing Wang, Ph.D., Drug Product Reviewer
Chandramouli Sithamalli, Ph.D., Drug Substance Reviewer
Suong Tran, Ph.D., Branch Chief (Drug Substance)
Joan Zhao, Ph.D., Biopharmaceutics Reviewer

Office of Program and Regulatory Operations
Rabiya Haider, PharmD., Regulatory Business Process Manager

Office of Process and Facilities
Djelila Mezaache, Ph.D., Process Reviewer

SPONSOR ATTENDEES

Jane Huang, MD.,	Chief Medical Officer, Hematology
Julie Boisvert, B.Sc.,	Director, Regulatory Affairs
Kirk Rosemark, B.Sc.,	Vice President, Regulatory Affairs
Wendy Yan, M.B.A.,	Senior Vice President, Global Head of Regulatory Affairs
Zhiwei Wang, Ph.D.,	Senior Vice President, Research Head of Chemistry
Tracy Tan, M.S., RAC,	Senior Manager, Regulatory CMC

Yiping Wang, Ph.D.,	Senior Director of PRD & Clinical Supply Chemistry (b) (4)
Zhengming Du, Ph.D.,	Senior Vice President, Head of CMC/Director for API Manufacturing & Logistics
Boudin Yiin, Ph.D.,	Senior Vice President, Global Head of Quality
Ying Ou, PhD.,	Senior Director, Clinical Pharmacology

1.0 BACKGROUND

BeiGene is proposing a New Drug Application for zabubrutinib (BGB-3111), an oral Bruton's tyrosine kinase (BTK) inhibitor for the indication of (b) (4) . Zanubrutinib previously was given orphan designation by the FDA for the treatment of mantel cell lymphoma (MCL), (b) (4)
BeiGene is requesting this Type B pre-NDA meeting to discuss aspects of the Chemistry, Manufacturing and Control information to be submitted in the NDA.

FDA sent Preliminary Comments to the sponsor on October 22, 2018.

2. DISCUSSION

Question 1:
Per the guidance provided during the December 2017 Type C meeting, BeiGene has developed and validated a dissolution method for quality control of zanubrutinib drug product. The method was submitted to the IND 125326 (Serial No. 0458, dated 05 Sept 2018) for FDA review and comment. Does the Agency agree with the proposed dissolution method?

FDA Response to Question 1:
Based on our preliminary review of the data in your submission serial No. 0458 (September 5, 2018) and No. 0471 (September 25, 2018), the selection of the proposed 0.5 % SDS in 0.1 N HCl as dissolution medium for the QC dissolution testing of the proposed drug product is not adequately justified. It appears that the dissolution medium with lower surfactant amount is more appropriate for your proposed Zanubrutinib capsules. However, please note that comprehensive review of the dissolution method development report is currently under review and additional FDA feedback will be provided within 3 months of your submission date of September 5, 2018.

Note that for future IND amendment seeking FDA feedback on the acceptability of the dissolution method, please send a follow-up email to OPQ project manager indicating your request, as this would help us accelerate our review assignment process.

Sponsor Response:

BeiGene acknowledges the FDA comments. Please note that BeiGene will hold our response pending FDA's comprehensive review of the dissolution method development. No additional discussion is requested at this time.

***Meeting Discussion*:**

The sponsor accepted FDA's response, no discussion occurred.

Question 2:

Zanubrutinib drug product from four manufacturers were used/distributed during the conduct of the pivotal Phase 1 clinical registrational trial BGB-3111-AU-003. The drug product batches manufactured by the intended commercial manufacturing site (b) (4) are being utilized in the confirmatory Phase 3 BGB-3111-302 clinical trial.

BeiGene has assessed comparability of the clinical batches used in the Phase 1 pivotal registrational study with the batches from the intended commercial manufacturing site based on:

- Dissolution profile comparisons
- Human PK comparisons

Does the Agency agree that dissolution profiles along with the human PK comparisons supports the bridging across the manufacturing sites?

FDA Response to Question 2:

The approach of using multimedia dissolution and human PK comparisons for bridging between the clinical batches and the registration batches from the intended commercial manufacturing site (Level 3 change) appears reasonable provided there are no Level 3 Process changes which require a BE study. Therefore, confirm that there are no changes which require BE study (refer to FDA Guidance for Industry: Immediate Release Solid Oral Dosage Forms Scale Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation). Include in your response, a schematic representation of the development of your proposed drug product from initial IND-product to the to-be-marketed product with all the formulation/manufacturing/process/etc. changes that occurred throughout development, the studies (in vitro or in vivo) bridging those products, and the PK, clinical, stability/registration studies in which those products were used. It is also noted that you have used an average of 3 lots for the reference batch to calculate f2 similarity values is not acceptable, f2 similarity calculation should be based on each lots. In addition to the mean dissolution data, individual vessel dissolution data as well as SD from each batch should be provided.

To support your proposed commercial drug substance manufacture, complete dissolution profiles of at least one batch of Zanubrutinib capsules using drug substance source of (b) (4) should be provided.

Sponsor Response:

BeiGene acknowledges the FDA comments. Please note that no Level 3 Process Changes were implemented through the drug product development process, nor at the proposed commercial manufacturing site. Furthermore, BeiGene will provide the individual f2 calculations for each batch.

Additionally, BeiGene will include the information requested above in the NDA package. No additional discussion is requested at this time.

***Meeting Discussion*:**
The sponsor accepted FDA's response, no discussion occurred.

Question 3:
Does the Agency agree with the stability proposal?

FDA Response to Question 3:
No, FDA does not agree with your stability proposal. At the time of original NDA submission, we recommend that you provide at least 9 months of long term stability data of three primary batches of the drug product and 6 months of stability data under accelerated conditions. The drug product primary batches should be manufactured using different drug substance batches. Refer to ICH Q1A(R2). The 12 months long term stability data should be submitted no later than 30 calendar days after the submission of the original NDA. The expiration dating period for the drug product will be assigned during the NDA review based on the totality of data provided in the submission.

Sponsor Response:
BeiGene acknowledges the FDA comments. To meet the criteria outlined in ICH Q1A(R2), BeiGene will provide the stability data package described below at the time of initial new drug application. The table also outlines the timing of additional stability data during the review process. BeiGene would like to highlight the inclusion of an additional drug product packaging presentation (80 caps per bottle).

The drug substance will continue to be manufactured by [redacted] (b) (4) however we will include their facility at [redacted] (b) (4) which has provided drug substance utilized in BGB-3111 clinical trials, in our new drug application. [redacted] (b) (4) utilizes the same quality systems and manufacturing process as [redacted] (b) (4)

Does FDA agree with our revised stability proposal?

DP Batch Number / Manufacturing Site	DP Batch Size (caps)	DS Lot Number / Manu Site / Batch Size	Packaging Config. Per bottle	Long term stability data @25°C/60 % RH			Accelerated stability data @40°C/75 % RH
				At time of NDA submission (March 2019)	Within 30 days of initial submission (April 2019)	Available during NDA Review (Data Available)	At time of NDA submission (March 2019)
[redacted] (b) (4)				18 m	24 m	24 m	6 m
				12 m	12 m	18 m (May 2019)	6 m
				12 m	12 m	18 m	6 m

DP Batch Number / Manufacturing Site	DP Batch Size (caps)	DS Lot Number / Manu Site / Batch Size	Packaging Config. Per bottle	Long term stability data @25°C/60 % RH			Accelerated stability data @40°C/75 % RH
				At time of NDA submission (March 2019)	Within 30 days of initial submission (April 2019)	Available during NDA Review (Data Available)	At time of NDA submission (March 2019)
[redacted] (b) (4)						(May 2019)	
				9 m	12 m	15 m (Aug 2019)	6 m
				6 m	9 m	12 m (Aug 2019)	6 m
				6 m	9 m	12 m (Aug 2019)	6 m
				6 m	9 m	12 m (Aug 2019)	6 m

[redacted] (b) (4)

Meeting Discussion:

Yes, FDA accepts the revised stability proposal. FDA informed the sponsor that due to the expedited timelines, we may not be able to review the new data if it is submitted late in the review cycle. The shelf life that will be assigned based on the totality of data available at the time of the review. Sponsor has the option to extend the shelf life based on real time data via annual reports.

Introduction of [redacted] (b) (4) ***drug substance site:***

FDA stated that the sponsor should compare manufacturing information from both drug substance sites - [redacted] (b) (4) **in the NDA submission, and provide a table to highlight any differences in the Manufacturing process and their effect on the quality of the drug substance.**

Question 4:
BeiGene intends to claim a categorical exclusion to the environmental assessment requirements in compliance with categorical exclusion criteria 21 CFR Part 25 .31 (b) applicable for action on an NDA when the estimated concentration of the drug substance at the point of entry into the aquatic environment will be below 1 part per billion. BeiGene claims that to the best of our knowledge no extraordinary circumstances exist.
Does the Agency agree?

FDA Response to Question 4:
FDA will need additional information before making a determination regarding whether the claim for a categorical exclusion from an environmental assessment (EA) per 21 CFR 25.31(b) is acceptable. This additional information should include a discussion of the substance's potential for aquatic effects, including those relevant to FDA's 2016 guidance, *Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity*, taking into account the substance's expected introduction concentration (EIC), mechanism of action, nonclinical and other toxicity data, plasma-based analysis (e.g., per Nallani et al., 2016), "read across" analysis with regard to other substances (including a summary of available data on measured or estimated concentrations and predicted no-effects concentrations (PNECs) of similar substances in the aquatic environment), and any other relevant and available information or environmental risk assessments. Submission of this information prior to the planned application will assist in the timely initiation of any needed assays should an EA be needed.
Reference: Nallani, G., Venables, B., Constantine, L., & Huggett, D. 2016. Comparison of Measured and Predicted Bioconcentration Estimates of Pharmaceuticals in Fish Plasma and Prediction of Chronic Risk. *Bulletin of environmental contamination and toxicology*, 96(5), 580-584.

Sponsor Response:
BeiGene acknowledges the FDA comments. No discussion requested at this time.

Meeting Discussion:
The sponsor accepted FDA's response, no discussion occurred.

Question 5:
In accordance with the Guidance for Industry, *M4Q: The CTD-Quality* (August 2001), the Facilities and Equipment section of the eCTD of Module 3 does not apply to New Molecular Entities. As such, relevant information related to the facilities and equipment, as needed, will be presented along with the information pertaining to the manufacturing and testing for the drug substance in 3.2.S.2, *Manufacture of Drug Substance*.
Furthermore, relevant information related to the facilities and equipment, as needed, will be presented along with the information related to the manufacture and testing of the drug product in 3.2.P.3, *Manufacture of Drug Product*. Section 3.2.A.1, *Facilities and Equipment*, will cross reference to the sections noted above.

Does the Agency agree with proposal?

FDA Response to Question 5:
Yes, the Agency agrees with your plans provided that by information related to testing, you mean in-process specification, analytical methods, and test results. Information related to final release testing should be submitted to P5 and S4 section for drug product and drug substance, respectively.

Sponsor Response:
BeiGene acknowledges the FDA comments. No discussion is requested at the meeting.

***Meeting Discussion*:**
The sponsor accepted FDA's response, no discussion occurred.

Question 6:
In accordance with 21 CFR Section 314.50, Content and format of an NDA, subsection c, BeiGene intends to submit one copy of the proposed master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product. The proposed master production record for the commercial manufacture of the drug substance is not planned to be submitted in the NDA. Does the Agency agree?

FDA Response to Question 6:
Yes, the agency agrees with your proposal. Proposed master production records for the manufacture of the drug substance are not required to be submitted in the NDA.

Sponsor Response:
BeiGene acknowledges the FDA comments. No discussion is requested at the meeting.

***Meeting Discussion*:**
The sponsor accepted FDA's response, no discussion occurred.

Additional Comment: Provide the mapping of which drug substance batches were used in the manufacture of drug product batches at the commercial drug product site and specify the lots used in each clinical study.

Sponsor Response:
BeiGene acknowledges the FDA comments. Please note that the information requested above will be included in the application. No discussion is requested at the meeting.

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/

ANAMITRO BANERJEE
11/02/2018