

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202429Orig1s016

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 121566

MEETING MINUTES

Genentech, Inc.
Attention: Agnes Blicq, PharmD
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Ms. Blicq:

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

We also refer to the meeting between representatives of your firm and the FDA on March 31, 2017. The purpose of the meeting was to discuss and obtain agreement on the content of a supplemental New Drug Application (sNDA) for ZELBORAF[®] in Erdheim-Chester disease (ECD).

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, please contact Jennifer Lee, Regulatory Project Manager, at (240) 402-4622.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
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: Pre-sNDA

Meeting Date and Time: Friday, March 31, 2017; 11:00 AM – 12:00 PM ET
Meeting Location: Teleconference

Application Number: IND 121566
Product Name: ZELBORAF[®] (vemurafenib)
Indication: Erdheim-Chester disease (ECD)
Sponsor/Applicant Name: Genentech, Inc. (GNE)

Meeting Chair: R. Angelo de Claro, MD
Meeting Recorder: Jennifer J. Lee, PharmD

FDA ATTENDEES

Office of Hematology and Oncology Products/Division of Hematology Products

Al Deisseroth, MD, PhD, Supervisory Associate Division Director
R. Angelo de Claro, MD, Clinical Team Leader
Tanya Wroblewski, MD, Clinical Reviewer
Nicholas Richardson, DO, MPH, Clinical Reviewer
Ashley Ward, MD, Clinical Reviewer
Theresa Carioti, MPH, Chief Project Management Staff
Jennifer Lee, PharmD, Regulatory Project Manager

Office of Biostatistics/Division of Biometrics V

Yuan-Li Shen, DrPh, Biometrics Team Leader
Che Smith, PhD, Biometrics Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V

Stacy Shord, PharmD, Clinical Pharmacology Team Leader
Sriram Subramaniam, PhD, Clinical Pharmacologist

SPONSOR ATTENDEES

Genentech, Inc.

Dawn Colburn, PharmD, Global Development Team Leader
Todd Riehl, PharmD, Clinical Science Lead

Martina Makrutzki, MD, International Medical Director
Marie Lou Munson, MD, Safety Science Leader
Weijiang Zhang, PhD, Clinical Pharmacologist
Ilsung Chang, PhD, Senior Statistical Scientist
Harper Forbes, MSc, Biometric Submission Team Lead
Erica Schleifman, PhD, Companion Diagnostics Project Leader
Seema Shah, MSc, Global Regulatory Leader
Agnes Bliccq, PharmD, Associate Program Director

Plexxikon Inc.

Meeta Vete, PhD, Senior Manager Regulatory Affairs

1.0 BACKGROUND

ZELBORAF[®] (vemurafenib) is a kinase inhibitor of several mutated forms of BRAF serine-threonine kinase, including BRAF V600E. It was the first approved product in its class, approved on August 17, 2011, for the treatment of unresectable or metastatic melanoma with the BRAFV600E mutation as detected by an FDA-approved test.

On March 18, 2016, a Type C meeting was held to discuss the clinical benefit of ZELBORAF[®] treatment for ECD, and to discuss the proposal to file a supplemental New Drug Application (sNDA) for ZELBORAF[®] in the treatment of BRAF-V600 mutation positive ECD [REDACTED] (b) (4) [REDACTED] using data from the VE-BASKET study MO28072. On August 2, 2016, orphan drug designation was granted for the treatment of ECD.

On January 9, 2017, the Sponsor requested a Pre-sNDA meeting to discuss and obtain agreement on the content of a sNDA for ZELBORAF[®] in ECD. FDA sent Preliminary Comments to Genentech on March 28, 2017.

2.0 DISCUSSION

Question 1: *The Sponsor believes that the clinically meaningful efficacy, along with the acceptable safety profile of vemurafenib in Study MO28072, supports a positive benefit-risk assessment for ECD (cohort 7) patients. Does the Agency agree?*

FDA Response to Question 1: **The topline efficacy and safety results appear to support demonstration of best overall response rate of 54.5%. The FDA will conduct our own analysis of efficacy and safety data to confirm and verify results to support a demonstration of a positive benefit-risk assessment.**

The indication to be granted will be determined during the review of the application. We note that enrollment in the ECD cohort was limited to ECD with the BRAF V600E mutation.

Discussion: *The Sponsor agrees to include scientific justification on the feasibility and necessity of a companion diagnostic for the proposed indication.*

Question 2: *The Sponsor believes that the data from Study MO28072 are sufficient to support full approval of a sNDA for the following indication:* (b) (4)
(b) (4), *Does the Agency agree?*

FDA Response to Question 2: We acknowledge receipt of the response to the information request regarding additional information on the V600E mutation testing. The Agency notes that the proposed indication population will be determined during the review process.

The determination of the type of approval will be made during the review process of the sNDA. Refer also to response to question 1.

Discussion: *The Agency acknowledges the revision of the proposed indication. The Sponsor will submit the revised indication for the pending Breakthrough Therapy Request.*

Question 3: *The efficacy and safety data to support the proposed update to the USPI will be based on the pivotal study MO28072. The Sponsor believes that the Summary of Clinical Safety (SCS) and Summary of Clinical Efficacy (SCE) will sufficiently summarize the overall safety and efficacy data.*

The Sponsor proposes to not provide pooled analyses of efficacy and safety, except for a pooled safety summary in the SCS for patients who received vemurafenib as monotherapy in Study MO28072.

Does the Agency agree with the Sponsor's proposal that the Integrated Safety Summary (ISS) and Integrated Efficacy Summary (ISE) in Module 5 will cross-refer to the SCS and SCE in Module 2?

FDA Response to Question 3: Your proposal to not pool efficacy and safety results except for pooled safety summary for patients from different cohorts from study M028072 is acceptable.

We recommend that you include a side-by-side safety analysis (Study M028072 and pooled vemurafenib monotherapy studies in malignant solid tumors) in the summary of clinical safety, including an assessment of safety issues noted as Warnings and Precautions in the Zelboraf USPI, as well as assessment for safety issues for hypertension, posterior reversible encephalopathy syndrome (PRES), and pancreatitis/increased lipase.

Include datasets for the ISS for subject demographics (ADSL format or equivalent), adverse events (ADAE format or equivalent), exposure (ADEX format or equivalent), laboratory data (ADLB or equivalent), and vital signs (ADVS format or equivalent).

Your proposal to have the ISE and ISS cross-reference the SCE and SCS, respectively, is acceptable provided that you do not exceed the page and size limits for the SCE and SCS.

Discussion: *The Agency agrees with the Sponsor's proposal to present three cohorts side by side in the ISS. The cohorts will include ECD (N=22 from MO28072), non-ECD (N=159 from MO28072), and metastatic melanoma (N=3219 from MO25515). The Sponsor agrees to provide datasets for these three cohorts. The Agency agrees with non-integration of the three cohorts, but recommended that the Sponsor clearly identify the data sets according to the three cohorts.*

Question 4: *Does the Agency agree with the proposal for the provision of:*

- *All raw efficacy datasets and all raw and derived safety datasets for all patients from each cohort in a legacy data format*
- *Efficacy derived datasets for ECD patients in a legacy data format*
- *Supporting specifications in the form of define .pdf files,*
- *eSub-ready annotated blank Case Report Forms (CRFs),*
- *Patient-level CRFs for all patients from each cohort,*
- *A reviewers' guide,*
- *Clinical Study Report (CSR) for Study MO28072?*

FDA Response to Question 4: **Yes, your proposal is acceptable. Include efficacy narratives for all 22 patients in the ECD population. In addition, include an updated swimmers plot in the clinical study report.**

The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the sNDA submission.

Discussion: *The Agency clarified that the sNDA should include efficacy narratives for the 22 patients. The Sponsor's proposal to supplement the narratives with available information from medical records is acceptable to the Agency.*

The Agency agrees to accept read-only SAS programs.

Question 5: *Given that vemurafenib has a well-characterized safety profile with an exposure of approximately 44,000 patients overall and because of the long duration of safety follow-up for ECD patients in Study MO28072, does the Agency agree with the Sponsor's proposal* (b) (4)

FDA Response to Question 5: **No,** (b) (4)
provide a 120 day safety update for the patients with ECD that continue to receive vemurafenib.

Discussion: *The Agency agrees with the Sponsor's proposal for the 120 day safety update, which would include follow-up from the eight patients with ECD in the extension study.*

Question 6: *Does the Agency agree that the planned sNDA for vemurafenib for the treatment of ECD qualifies for Priority Review?*

FDA Response to Question 6: **A decision on the review timeline will be made after the filing determination of the sNDA.**

Discussion: *No discussion occurred.*

Question 7: *Does the Agency have any other comments on the proposed contents of the sNDA?*

FDA Response to Question 7:

From a technical standpoint (not content related) the proposed Table of Contents for the planned sNDA is acceptable. However, apply the following comments:

- 1. A single PDF file of all the documents in Module 1.3.4 or, individual pdf files of each document can be provided in Module 1.3.4, with proper bookmarks, table of contents, hyperlinks and leaf title(s). Do not create additional nodes (e.g. Module 1.3.4.1, Module 1.3.4.2 - Module 1.3.4.5).**
- 2. List of investigators should reside in Module 5 (not Module 1.3.4), under the study tagging file (STF) of the respective study and tagged as "list-description-investigator-site".**
- 3. For archival purposes, also submit a PDF file of any document submitted in Word. When Word documents are submitted, make sure the leaf title includes "Word", so reviewers can quickly identify the Word version of the document.**
- 4. Case Report Forms need to be referenced under the appropriate study tagging file (STF) of the study they belong, organized by site as per the specifications and tagged as "case report form". Please refer to *The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008)*, found at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>.**

Clinical

- 1. The Agency requests submission of the diagnostic pathology and molecular diagnostic reports for the 22 patients who were enrolled in the ECD cohort.**

Clinical Pharmacology

1. In the Summary of Clinical Pharmacology, also address the basis for selecting the dose and dosing regimen used in the registration trial.
2. Include the summary of the bioanalytical methods in Module 2.7.1, and PK/PD analysis reports and data sets in Module 5.3.5.3 (refer to Comment 3e for further details), in addition to the proposed clinical pharmacology information.
3. Apply the following advice in preparing the clinical pharmacology sections of the sNDA submission:
 - a. Submit validation and bioanalytical reports for the bioanalytical method(s) used in Study MO20872.
 - b. Provide complete pharmacokinetic datasets for Study MO20872. The patients' unique ID in the pharmacokinetic datasets should be consistent with those in datasets submitted for clinical review.
 - i. Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - ii. Identify individual patient with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets. Provide the relevant descriptive statistics for each of these variables in support of the proposed dose in the Summary of Clinical Pharmacology.
 - c. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean \pm standard deviation) and median with range as appropriate in the final study report.
 - d. Submit information and data to support the population pharmacokinetic analysis.

Refer to the pharmacometric data and models submission guidelines found at <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm> and the Guidance for Industry found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf> for more information.
 - e. Submit the results of exposure-response (measures of effectiveness, biomarkers and toxicity) analyses for vemurafenib in the indicated patient population in the sNDA submission, including an assessment of the effect of covariates on the exposure-response relationships. Refer to Guidance for Industry found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf> for more information.

***Discussion:** The Agency notes that it will be important that the pathologic diagnosis be documented for the 22 patients, and the information should be submitted with the sNDA.*

The Agency notes that the Sponsor will provide an assessment of the effect of tumor type on PK using all available data from MO28072.

Additional Discussion: The Agency clarified that the OSI request only applies to the ECD sites.

The Agency provided clarification on pathology evaluation for dermatopathology specimens collected in the clinical trial. The Agency would be interested with the assessment ECD of the specimens at baseline and the assessment for skin malignancies other than ECD on the follow-up specimens. The Agency notes that the pathologic documentation of the diagnosis of ECD may be established on other specimens as discussed in question 7.

The Sponsor indicated that they plan to submit the sNDA approximately at the end of June 2017.

3.0 OTHER IMPORTANT MEETING INFORMATION

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

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).

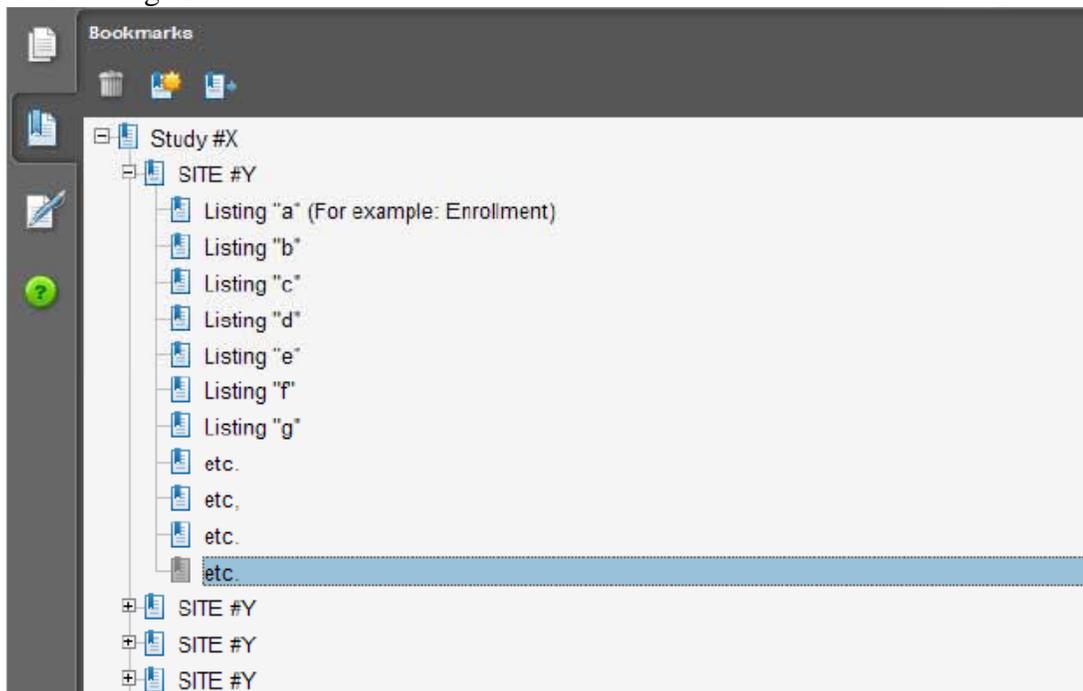
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)

- 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 Item¹	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.

¹ Please see the OSI Pre-NDA/BLA 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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Submit the proposed revision to the indication for the pending Breakthrough Therapy Request	Sponsor	ASAP (given the pending Breakthrough Therapy Request is under review)

6.0 ATTACHMENTS AND HANDOUTS

Attached is a copy of Genentech's response to FDA's Meeting Preliminary Comments, received via email from Agnes Bliccq on March 30, 2017.

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

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

/s/

ROMEO A DE CLARO
03/31/2017