CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761150Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 107768

MEETING MINUTES

MacroGenics, Inc.
Attention: Maria Petkoski
9704 Medical Center Drive
Rockville, MD 20850

Dear Ms. Petkoski:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for margetuximab (MGAH22).

We also refer to the meeting between representatives of your firm and the FDA on May 6, 2019. The purpose of the meeting was to discuss your plans for clinical and nonclinical format and content of a margetuximab BLA (b) (4)

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, contact Clara Lee, Regulatory Project Manager at (240) 402-4809 or Clara.Lee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Clara Lee, PharmD
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation and Research

Harpreet Singh, MD
Clinical Team Leader (Acting)
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: May 6, 2019 / 9:00 AM – 10:00 AM
Meeting Location: FDA White Oak Campus
Building 22 – Room 1311

Application Number: IND 107768
Product Name: Margetuximab (MGAH22)
Indication: (b) (4)

Sponsor Name: MacroGenics, Inc.

Meeting Chair: Harpreet Singh, MD
Meeting Recorder: Clara Lee, PharmD

FDA ATTENDEES

Julia Beaver, MD, Director, DOP1
Harpreet Singh, MD, Clinical Team Leader (Acting), DOP1
Tatiana Prowell, MD, Clinical Reviewer, DOP1
Preeti Narayan, MD, Clinical Reviewer, DOP1
Lijun Zhang, PhD, Biometrics Team Leader (Acting), DBV
Anup Amatya, PhD, Biometrics Reviewer, DBV
Tiffany Ricks, PhD, Supervisory Pharmacologist/Toxicologist Reviewer, DHOT
George Ching-Jey Chang, PhD, Pharmacologist/Toxicologist Reviewer, DHOT
Huiming Xia, PhD, Clinical Pharmacology Reviewer, DCPV
Rosane Charlab Orbach, PhD, Genomics Team Leader, OCP
Jeffery Kraft, PhD, Genomics Reviewer, OCP
Clara Lee, PharmD, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES

Sam Hong, PhD, Senior Director, Biostatistics
Neely Galedd Horak, Associate Program Management Director, Business Development & Portfolio Management
(b) (4) Clinical Pharmacology Consultant
Kenneth Jacobs, MD, Executive Director, Product Safety
Daniel Mannix, PhD, Vice President, Regulatory Affairs
Jeffrey Nordstrom, PhD, Director, Preclinical Product Development
Maria Petkoski, Director, Regulatory Affairs
Edwin Rock, MD, Vice President, Clinical Research

Pierre Verroye, Vice President, Data Management, Programming, & Biostatistics
Jon Wigginton, MD, Senior Vice President, Clinical Development and Chief Medical Officer

1.0 BACKGROUND

Post-Meeting Note: Sponsor noted a typographical error in the background section in the preliminary comments sent on April 30, 2019. This is a revised version.

The sponsor has requested a type B pre-BLA meeting to discuss the clinical and nonclinical format and content of a proposed BLA for margetuximab.

The sponsor is seeking the following indication for margetuximab:

- (b) (4)

Margetuximab (MGAH22) is a chimeric (b) (4) Fc-engineered, immune-activating IgG1 monoclonal antibody derived from 4D5, the murine precursor to trastuzumab, that binds the HER2 oncoprotein. It is being studied under IND 107768 for the treatment of HER2-positive carcinomas.

The sponsor's development program in breast cancer includes one ongoing and two completed clinical studies. A Phase 1 study CP-MGAH22-01 (Study 01) that evaluated margetuximab in patients with relapsed/refractory HER2+ breast cancer and other HER2+ carcinomas. In Study 01, 66 patients received treatment with margetuximab monotherapy. Among the 24 evaluable patients with HER2+ metastatic breast cancer, there were confirmed partial responses (PRs) in four patients. A Phase 2 study CP-MGAH22-02 (Study 02) evaluated margetuximab in patients with HER2-low relapsed/refractory breast cancer but was stopped early (b) (4). Study 04, "A Phase 3, Randomized Study of Margetuximab Plus Chemotherapy vs Trastuzumab Plus Chemotherapy in the Treatment of Subjects with HER2+ MBC Who Have Received Prior Anti-HER2 Therapies and Require Systemic Treatment" is an ongoing Phase 3 study of margetuximab plus chemotherapy in patients with previously treated HER2+ MBC. Study 04 is intended to serve as the registration trial for the proposed BLA submission.

Study 04 is a Phase 3 randomized, open-label, comparator-controlled study of margetuximab versus trastuzumab, both in combination with chemotherapy of physician's choice, for the treatment of patients with previously treated advanced HER2+ breast cancer. Participants must have received at least 2 prior lines of HER2-directed therapy in the metastatic setting, or for patients who received (neo)adjuvant pertuzumab, at least 1 prior line of HER2-directed therapy in the metastatic setting. In addition, participants must have received at least 1, and no more than 3, prior regimens of therapy overall in the metastatic setting.

Eligible patients were randomized 1:1 to receive chemotherapy of physician's choice plus either margetuximab 15 mg/kg IV Q3W or trastuzumab 8 mg/kg loading dose, 6 mg/kg subsequent doses, IV Q3W. Randomization was stratified by number of metastatic sites (≤2, >2), number of prior regimens of therapy for metastatic disease (≤2, >2), and chemotherapy chosen. Prior to randomization to either margetuximab or trastuzumab, investigators selected one of four backbone chemotherapy regimens given at standard doses: capecitabine, eribulin, gemcitabine, or vinorelbine. Subjects were treated until disease progression, death, withdrawal of consent, or investigator/patient decision. Following study drug discontinuation, participants continue to be followed for survival.

The primary objective of Study 04 was to evaluate the efficacy of chemotherapy plus margetuximab versus chemotherapy plus trastuzumab. The study includes two primary endpoints, progression-free survival (PFS) and overall survival (OS), which are assessed in sequential order. Additional endpoints included investigator-assessed PFS, objective response rate (ORR) by independent review, health-related quality of life, clinical benefit rate (CBR), duration of response (DoR), ADA directed against margetuximab, investigator-assessed ORR, safety profile, PPK and E-R features of margetuximab in breast cancer, and effect of allelic variation in CD16A, CD32A, and CD32B on the efficacy of margetuximab.

The primary PFS analysis was to occur after 257 PFS events had been observed. This design provided 90% power to demonstrate a 2 month improvement in median PFS from 4 to 6 months (hazard ratio [HR] 0.67) with a 2-sided alpha of 0.05.

Study 04 enrolled 536 patients at approximately 200 trial sites globally. All participants had previously received trastuzumab, all but one had previously received pertuzumab, and approximately 90% had previously received T-DM1. The data cutoff date for the primary PFS analysis and first interim analysis of OS was October 10, 2018, at which time 536 patients had been enrolled and 265 events had been observed. The stratified HR for PFS by independent review was 0.76 (0.59, 0.98); p = 0.033, corresponding to a 0.9 month improvement in median PFS from 4.9 to 5.8 months. Overall survival data are immature with 158 deaths observed at the time of the data cutoff. The HR for OS was 0.95 (0.69, 1.31), p=0.76. The second planned interim analysis of OS is anticipated in August 2019 when 270 (70% information fraction) of the 385 required

deaths have occurred. The final planned OS analysis will occur in approximately May 2020 once 385 deaths have been observed.

There were more all-grade drug-related adverse reactions (57% versus 48%) and grade ≥3 drug-related adverse reactions (12% versus 8%) in the chemotherapy plus margetuximab arm than in the chemotherapy plus trastuzumab arm. Drug-related serious adverse events (1.5% in each arm) and fatal adverse events (0.4% in each arm) were rare and occurred in equal numbers of patients in the two arms. The most common adverse events were myelosuppression, gastrointestinal toxicity, fatigue, and hyperpyrexia.

Margetuximab is also being studied in combination with pembrolizumab (b) (4) for patients with relapsed/refractory advanced HER2+ gastroesophageal junction or gastric cancer (b) (4)

FDA sent Preliminary Comments to MacroGenics, Inc. on April 30, 2019.

2. DISCUSSION

Question 1: Does FDA agree that Study 04 Phase 3 efficacy and safety results are adequate to support filing and review of a BLA for margetuximab for the MBC indication?

FDA Response to Question 1: While the application may be appropriate for filing and review, we have the following substantial concerns:

- **The observed absolute difference in median PFS is very small and less than the imaging assessment interval.**
- **The OS HR approaches 1 with wide confidence interval and immature data.**
- **Margetuximab has greater toxicity than trastuzumab based upon the preliminary data in the background package.**

Sponsor Response to Question 1: MacroGenics would like to discuss other potential options for when to submit the 2nd interim OS data and data from the SOPHIA infusion substudy (Questions 1, 3, 4, and 6 discussed together).

Meeting Discussion: The sponsor provided updated OS medians based on an unplanned look at the number of survival events from a data cutoff of April 2019.

The agency reiterated concerns regarding the overall risk-benefit profile of the planned BLA submission, in particular, the small magnitude of PFS benefit and immature OS data.

The sponsor proposed submitting updated AE data based on the April 2019 cutoff in the original BLA submission. The primary PFS datasets and CSRs will be based on the October 2018 data cutoff. They plan to submit the BLA with the second interim analysis of OS estimated in August/September 2019 with the original submission. The agency stated that this is acceptable.

The agency recommends submission of a robust dataset for the infusion sub-study at the time of the original BLA submission.

The agency stated the application may require discussion at an Oncologic Drugs Advisory Committee (ODAC) meeting.

Post-Meeting Comment: Please note that unplanned looks of OS data by treatment arms may cause type I error rate inflation.

Question 2: MacroGenics will make radiographic images from central blinded review available on request during BLA review. Does FDA agree?

FDA Response to Question 2: Yes.

Meeting Discussion: No discussion took place.

Question 3: Does FDA agree with the proposed data cutoff date for the BLA submission?

FDA Response to Question 3: No, we would recommend that you use an August 2019 data cutoff date for the BLA submission (i.e., data cutoff date when the second interim analysis of OS has occurred) given the very modest absolute improvement in median PFS observed in Study 04, the increased toxicity profile, and the HR of 0.95 for OS at the first interim analysis of OS. This analysis would give greater confidence that there is not a detriment to OS. See FDA Response to Question 6.

Sponsor Response to Question 3: MacroGenics would like to discuss other potential options for when to submit the 2nd interim OS data and data from the SOPHIA infusion substudy (Questions 1, 3, 4, and 6 discussed together).

Meeting Discussion: See Meeting Discussion to Question 1.

Question 4: Does FDA agree with the proposed approach to the safety update?

FDA Response to Question 4: No. See FDA Response to Question 3.

Sponsor Response to Question 4: MacroGenics would like to discuss other potential options for when to submit the 2nd interim OS data and data from the SOPHIA infusion substudy (Questions 1, 3, 4, and 6 discussed together).

Meeting Discussion: See Meeting Discussion to Question 1.

Question 5: Does FDA agree with proposed content of the ISS, as described in the ISS SAP?

FDA Response to Question 5: Yes. Please also include in the initial BLA submission autopsy reports for any patients in studies of margetuximab in whom an autopsy was performed.

Meeting Discussion: No discussion took place.

Question 6: Does FDA agree with proposed provisions of Study 04 Infusion Substudy data, including data presentations?

FDA Response to Question 6: See FDA Response to Question 3. An August 2019 data cutoff would also provide a larger body of data to assess the dose regimen used in the Study 04 Infusion Substudy that you propose to include in labeling.

Sponsor Response to Question 6: MacroGenics would like to discuss other potential options for when to submit the 2nd interim OS data and data from the SOPHIA infusion substudy (Questions 1, 3, 4, and 6 discussed together).

Meeting Discussion: See Meeting Discussion to Question 1.

Question 7: Does FDA agree that potential risks with margetuximab can be managed through product labeling and routine pharmacovigilance surveillance without need for a REMS or Medication Guide?

FDA Response to Question 7: This would be determined at the time of the review of the complete BLA submission.

Sponsor Response to Question 7: MacroGenics understands that the need for a REMS/medication guide is a review issue. With that said, it was MacroGenics' understanding from the Meeting Granted Letter that the Company should discuss and reach agreement at the preBLA meeting whether a REMS or other risk management actions is warranted. As such, can FDA share any thoughts on whether a REMS might be warranted for margetuximab?

Meeting Discussion: The necessity for REMS will be a review issue, however is unlikely given the preliminary safety data provided in the background package.

Question 8: Does FDA agree that a pregnancy registry is not warranted at this time for margetuximab?

FDA Response to Question 8: Yes.

Meeting Discussion: No discussion took place.

Question 9: MacroGenics believes that the Study 04 data support a clinical benefit for the entire patient population but notes an increased benefit in patients who are CD16A F allele carriers for the prespecified exploratory analysis. Does FDA have any comments?

FDA Response to Question 9: The absolute improvement in median PFS in the ITT population of less than one month is extremely modest. All prespecified subgroup analyses without alpha allocated, including the assessment of efficacy in patients who are CD16A F allele carriers, are considered hypothesis-generating and no inference may be drawn. We note the HR of 1.78 (95% CI: 0.87, 3.62) in the CD16A/VV subgroup of 69 patients. Please include subject-level genotype data for all patients for CD16A, CD32A, and CD32B at the time of your BLA submission, as well as detailed patient disposition data within CD16A for each of the pre-specified subgroups.

Question 10: Does FDA agree that clinical pharmacology studies listed herein are sufficient to support filing and review of the BLA?

FDA Response to Question 10: Yes.

Meeting Discussion: No discussion took place.

Question 11: Does FDA agree that MacroGenics' approach to PPK and E-R analysis plan is adequate to support filing and review?

FDA Response to Question 11: Your proposal seems reasonable. The acceptability of your proposed dosing regimen is a review issue. See also FDA Response to Question 6.

Meeting Discussion: No discussion took place.

Question 12: Does FDA agree that immunogenicity can be adequately assessed in the Summary of Clinical Pharmacology Studies (Module 2.7.2) and that a standalone Integrated Summary of Immunogenicity (ISI) will not be required?

FDA Response to Question 12: Your proposal is acceptable.

Meeting Discussion: No discussion took place.

Question 13: Does FDA agree that the nonclinical package for margetuximab is sufficient to support the BLA filing and FDA review?

FDA Response to Question 13: Your proposed nonclinical package for margetuximab appears sufficient to support your BLA submission. The final determination will be made after we have received your BLA. Data to support labeling should be based on findings from margetuximab or non-product specific published literature. You may not rely on FDA's previous findings of safety and efficacy or product specific data for which you do not have a written right of reference to support a 351(a) BLA submission.

Meeting Discussion: No discussion took place.

Question 14: Does FDA agree that SEND datasets for toxicology studies are not required and that submission of the Trial Summary data file is sufficient to support this BLA filing?

FDA Response to Question 14: Yes.

Meeting Discussion: No discussion took place.

Question 15: Does FDA agree that safety and efficacy data summarized in the briefing package justify a request for priority review of the proposed BLA?

FDA Response to Question 15: Decisions to grant priority or standard review are made at the time of filing; however, the current PFS and first interim OS results would not justify priority review of the proposed BLA.

Meeting Discussion: No discussion took place.

Question 16: Does FDA agree that overall contents of the proposed application are adequate for filing and review?

FDA Response to Question 16: A decision on the adequacy of the application for filing and review will be made at the time of the BLA submission.

Meeting Discussion: No discussion took place.

Question 17: Does FDA recommend an Application Orientation Meeting after BLA submission to outline major components of the submission?

FDA Response to Question 17: Yes.

Sponsor Response to Question 17: Can the Agency provide guidance on the scope and logistics for this meeting? It is our understanding that the purpose of an AOM meeting was initially to discuss content/format (as per the CDER NDA/BLA Desk Reference Guide), but now includes the sponsor making a presentation on the risk / benefit profile of the product.

Meeting Discussion: FDA provided guidance on the components of an AOM. Further information will be provided to the sponsor.

Question 18: Does FDA agree that cross-application hyperlinking and referencing is acceptable for the proposed BLA filing?

FDA Response to Question 18: Yes.

Meeting Discussion: No discussion took place.

Question 19: Is it acceptable to FDA CDER (i.e., for BLA filing) and Office of Compliance (i.e., for Bioresearch Monitoring [BIMO] requirements) that MacroGenics submits the latest version of a document (e.g., Clinical Protocol, SAP) with a Summary of Changes, rather than including all versions of a document?

FDA Response to Question 19: No. You should provide in your initial BLA submission all versions of the protocol and SAP as appendices, or a link to them, in addition to a Summary of Changes. In addition to the versions of the protocol and SAP, all other requested BIMO documents should be submitted to your BLA.

Meeting Discussion: No discussion took place.

ADDITIONAL COMMENTS: For Study 04, your efficacy datasets should include variables to delineate for each patient the following: overall number of lines of therapy in the metastatic setting, number of lines of HER2-directed therapy in the metastatic setting, overall number of lines of HER2-directed therapy (i.e., both

(neo)adjuvant and metastatic setting), whether or not patients have previously received T-DM1, in which setting pertuzumab was received (i.e., (neo)adjuvant versus metastatic), and whether or not the stage at initial presentation was stage 4 (i.e., de novo metastatic breast cancer). In addition, please include in the Clinical Study Report detailed analyses of the primary and key secondary efficacy endpoints for the prior therapy subgroups noted above.

Meeting Discussion: No discussion took place.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our March 5, 2019 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]

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. These items were addressed in the preliminary comments and captured meeting discussion.

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

- 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. Refer to Meeting Discussion for Question 7.

- 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.

In addition, we note that a chemistry pre-submission meeting was held on May 6, 2019. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

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.[2]

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.[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.

[2] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm544641.htm
[3] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm
[4] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[5] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

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

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

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.[6]

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.[7]

[6] http://www.fda.gov/ectd
[7] 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).

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*.[8]

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

[8] https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf

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

- AssessmentAid[10]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

Your proposed 351(a) BLA would be within the scope of this guidance. As such, FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Not applicable.

[9] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612927.htm
[10] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612923.htm

5.0 ACTION ITEMS

1. **Additional information on Application Orientation Meetings will be provided.**

6.0 ATTACHMENTS AND HANDOUTS

1. **SOPHIA OS Results Based on Data as of 30APR2019 (provided by MacroGenics, Inc. on May 6, 2019)**
2. **OCE's General Advice for Application Orientation Meetings**

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

OCE's General Advice for Application Orientation Meetings

FDA may hold an Application Orientation meeting with the Applicant following submission of a new NDA, original BLA, or efficacy supplement, for purposes of orienting the review team to the content and format of the application. The meeting is generally held within 45 days of application submission. Please note, individuals from Centers for Medicare and Medicaid Services (CMS) may be in attendance for observational purposes. CMS and FDA have a Memorandum of Understanding to promote information sharing. Trade secret and other confidential commercial information are protected from unauthorized disclosure.

The following advice is intended to aide you in your AOM presentation preparation. This list is not inclusive of all issues to consider, as individual applications have unique characteristics. We also acknowledge that information needed to support a new NDA or original BLA will differ from an efficacy supplement. If you believe some comments are inapplicable to your application and therefore your presentation and/or you believe that other information is relevant, adjust your presentation accordingly.

AOMs are generally one hour in length, including time for discussion and Q & A (35-40 minutes for presentation maximum, 25-20 minutes for discussion).

The AOM may be followed by a separate 30-60 minute meeting to address technical aspects of the application limited to members of the review team, including a walk-through of the datasets.

The primary focus of the AOM presentation should be the risk/benefit profile of the product (with clinical sections presented first) and highlights of other sections to follow (1-2 slides each for remaining sections).

Administrative:

1. Sponsor attendees

2. Presentation outline - list sections included in submission.

Background and Application Specifics:

3. Proposed indication(s), current indication(s) for an efficacy supplement, and dosing recommendation(s) for the proposed indication in proposed labeling

4. Risk/benefit profile for drug/biologic

5. Drug/biologic characteristics, including what makes drug/biologic unique, mechanism of action

6. Listing of major efficacy trial(s) to support application, as well as dose-finding and activity-estimating trials supporting the proposed indication and the safety assessment.

7. Statement of whether you plan to seek accelerated approval or regular approval, if accelerated approval, design of the confirmatory trial(s) that will be ongoing at the time

of accelerated approval and a timetable for trial completion and final clinical study report submission

Summary Content of NDA/BLA/Efficacy Supplement Sections:

8. Clinical/Statistics:
    - Description of clinical trial design, including statistical analysis plan;
    - Key findings from registration trials:
        - Minimum length of follow-up
        - Demographics (including region) of subjects and baseline prognostic characteristics. NOTE: For demographics, address whether your study(s) represent ethnic minorities and whether study population is reflective of the U.S. population in which the drug/biologic is intended to be used.
        - Outcomes from primary and secondary endpoints
        - Subpopulation analyses of safety and efficacy by age, sex, race, concurrent therapy, number of prior treatments, and/or region/country if applicable
        - Safety findings (most frequently reported adverse events, serious adverse events) including safety findings from trials in other phases, risk mitigation strategies for adverse reactions

    Present results of the following, as appropriate:
    - Biomarker development for population selection (if applicable)
    - Assay validation (if applicable)

    120-day Safety update: Plans including how many additional patients will be included in safety update and from which studies

In absence of unique application circumstances, the following sections should be limited to 2 slides or less:

9. CMC: Manufacturing site locations, dates available for inspection, brief summary of manufacturing process, comparability of drug substance (DS) and drug product (DP) after major manufacturing changes, characterization, controls, stability, status of drug master files, any novel excipients, state if application is Quality by Design (ICH Q8, Q9, Q10)
    - For BLAs: Immunogenicity results, validated assay method, and manufacturing schedule for DS and DP.

10. Nonclinical: Brief summary of toxicology studies and findings, genetic toxicology, QT studies, effect on fertility or reproduction, carcinogenicity studies (if needed), qualification of drug impurities

11. Clinical Pharmacology: Exposure response relationship supporting dose selection, pharmacogenomics-related issues, description/listing of PK studies, PK characteristics (metabolic pathway, metabolites, $t_{1/2}$, ADME, PK in special populations, drug-drug interactions)

12. If a Risk Evaluation and Mitigation Strategy (REMS) is included, briefly identify the risks to be addressed, list the goals of the REMS, and outline the REMS components

(Medication Guide, Communication Plans and/or Elements to Assure Safe Use (ETASU).

13. Summary

14. Q & A

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/

CLARA J LEE
05/30/2019 09:25:43 AM

B HARPREET SINGH
05/30/2019 03:58:07 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 107768

MEETING MINUTES

MacroGenics
Attention: Kristin A. Phillips
9640 Medical Center Dr.
Rockville, MD 20850

Dear Ms. Phillips:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for margetuximab (MGAH22).

We also refer to the meeting between representatives of your firm and the FDA on January 30, 2015. The purpose of the meeting was to hold an End of Phase2/Pre-Phase 3 meeting to discuss your proposed clinical development plan.

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 Jeannette O'Donnell, Regulatory Project Manager at (240) 402-4978 or email: Jeannette.Odonnell@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Patricia Cortazar, M.D.
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	January 30, 2015; 3:00 – 4:00 pm
Meeting Location:	FDA White Oak 22, Room 1311
Application Number:	IND 107768
Product Name:	Margetuximab (MGAH22)
Indication:	Breast Cancer
Sponsor/Applicant Name:	MacroGenics
Meeting Chair:	Patricia Cortazar, M.D.
Meeting Recorder:	Jeannette O'Donnell

FDA ATTENDEES

Amna Ibrahim, M.D., Acting Director, DOP1
Geoffrey Kim, M.D., Acting Deputy Director, DOP1
Patricia Cortazar, M.D., Clinical Team Leader, DOP1
Julia Beaver, M.D., Clinical Reviewer, DOP1
Gwynn Ison, M.D., Clinical Reviewer, DOP1
Tatiana Prowell, M.D., Clinical Reviewer DOP1 (by phone)
Qi Liu, PhD., Clinical Pharmacology Team Leader, DCP5
Pengfei Song, Ph.D., Clinical Pharmacology Reviewer, DCP5
Todd Palmby, Ph.D., Supervisory Pharmacologist/Toxicologist, DHOT
Shenghui Tang, Ph.D., Biometrics Team Leader, DBV
Lijun Zhang, Ph.D., Biometrics Reviewer, DBV
Jeannette O'Donnell, Regulatory Project Manager, DOP1
Sakar Wahby, Pharm.D., Regulatory Project Manager, DOP1
Pamela Balcazar, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES

Jennifer Brown, Ph.D., Toxicologist
David Carlin, Ph.D., V.P. Biostatistics
Robert Lechleider, M.D., V.P., Clinical Research
Jeff Nordstrom, Ph.D., Director, Research and Development
Maria Petkoski, Associate Director, Regulatory Affairs

Kristan Phillips, V.P., Regulatory Affairs
Kathryn Stein, Ph.D., Senior V.P., Product Development and Regulatory Affairs
Jon Wigginton, M.D, Senior V.P., Clinical Development
(b) (4)., Pharmacokinetics Consultant
(b) (4) Clinical Consultant (by phone)

1.0 BACKGROUND

This Type B Meeting will address the clinical development plan of margetuximab (MGAH22). Specifically, plans related to a Phase 3 registration trial "A Phase 3, Randomized, Active Control Study of Margetuximab plus Chemotherapy vs. Trastuzumab plus Chemotherapy in the Treatment of Patients with HER2+ Metastatic Breast Cancer Who Have Received Two Prior Anti-HER2 Therapies and Require Systemic Treatment" will be discussed.

Margetuximab is an IgG1 anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody being developed under IND 107768 for the treatment of HER2+ carcinomas with no available standard therapy. This meeting will discuss the proposed indication of margetuximab (b) (4)

Current clinical studies under this IND include a Phase 1 dose escalation study of MGAH22 in patients with refractory HER2 positive breast cancer and patients with other HER2 positive carcinomas for whom no standard therapy is available and a Phase 2 single arm open-label study in patients with relapsed or refractory advanced breast cancer whose tumors express HER2 at a IHC 2+ and lack FISH amplification. (b) (4) is being investigated in HER2+ adenocarcinoma of the stomach or GE junction.

The Phase 3 protocol under discussion is Protocol CP-MGAH22-04, a randomized, open-label, controlled study planned in 530 women. CP-MGAH22-04 is proposed to randomize patients with advanced HER2+ breast cancer who have been treated with two prior lines of anti-HER2-containing therapy to either margetuximab plus chemotherapy or trastuzumab plus chemotherapy. The chemotherapy is selected by doctor's choice ahead of randomization. The primary objectives for this study are PFS by central radiology review and OS. Secondary objectives are investigator-assessed PFS and objective response rate. In addition other secondary endpoints include CBR, HRQoL, PK and safety profile.

FDA sent Preliminary Comments to MacroGenics on January 26, 2015.

2.0 CLINICAL

Question 1 - Patient population
The proposed Phase 3 pivotal study will enroll patients with HER2+ metastatic breast cancer (MBC) who have received at least two prior lines of anti-HER2-containing therapies and require systemic treatment. At least one prior line must have been in the metastatic setting (b) (4)

[redacted]. Does FDA agree that the population to be targeted by this proposed trial represents an unmet medical need that could serve as the basis for submitting a BLA seeking a specific indication in this setting?

FDA Response to Question 1:

No, the proposed population as currently defined does not represent a medical need. Currently there are anti HER2 therapies that confer overall survival. The patient population should be redefined. [redacted]

Meeting Discussion:

The sponsor proposed the following population: " [redacted] **." The Agency agreed.**

Question 2 - Suitability of trastuzumab as a comparator

Does FDA agree that trastuzumab plus chemotherapy would be an acceptable comparator in the proposed Phase 3 margetuximab study in patients with HER2+ breast carcinoma who have received at least two prior anti-HER2-containing therapies and who require systemic treatment as defined in the accompanying clinical study protocol?

FDA Response to Question 2:

Yes, if the population is redefined as described in our response to Question #1.

Question 3 - Chemotherapy options

Does FDA agree that it is permissible to allow investigators to choose from available standard chemotherapy regimens to be used as the chemotherapy backbone?

FDA Response to Question 3:

Yes. However, you should select from a few pre-specified chemotherapy options using conventional doses. Please provide available safety data of margetuzimab with the proposed chemotherapy combinations if available. Otherwise, DMC should provide close monitoring for tolerability of the combinations.

Meeting Discussion:

The sponsor agreed to select four pre-specified chemotherapy options using conventional doses as used in combination with trastuzumab and will stratify for these chemotherapy options. A rationale for the selection of the doses will be provided in the protocol. The data safety monitoring committee will evaluate the individual chemotherapy options across both arms at regular intervals and as needed.

Question 4 - Justification of the clinical dose

Does FDA agree that a dose of 15 mg/kg administered every 3 weeks is acceptable for the proposed Phase 3 study?

FDA Response to Question 4:

We cannot respond to this question as you provided data from only 6 patients treated at the 15 mg/kg administered every 3 weeks dose level. You should justify the proposed dose with additional safety data and plan safety stopping rules in the proposed Phase 3 trial particularly for cardiac adverse reactions. As the development of margetuximab progresses, we strongly recommend that you pool available dose, pharmacokinetic, pharmacodynamic, efficacy, and safety data in order to conduct an integrated dose-response and exposure-response analyses for dose optimization. We recommend that you update these dose-response and exposure-response analyses as more data becomes available. Such an approach to dose selection will help you design pivotal trials.

Meeting Discussion:

The sponsor updated the Agency to the further patients who had been treated at 15 mg/kg every 3 weekly dosing. They have a total of 48 patients treated with no cardiac safety signals at comparable exposure. The sponsor clarified their plan for cardiac monitoring and safety stopping rules in the proposed Phase 3 trial, as based on the Herceptin label. The sponsor will be providing additional dose justification within the final protocol.

Question 5 - trastuzumab dosing schedule

Does FDA agree that it would be acceptable to administer trastuzumab every 3 weeks in combination with chemotherapy in the proposed clinical study?

FDA Response to Question 5:

Yes.

Question 6 - Study design

MacroGenics proposes to perform an open-label study with two primary endpoints assessed in sequential order. The first endpoint of PFS will be determined by a blinded, independent central radiology review. The second primary endpoint is OS. Does FDA agree that an open-label (sponsor, site, and patient unblinded), active control study design with 1:1 randomization and blinded central radiology review for PFS assessment, would be appropriate for the proposed Phase 3 margetuximab trial?

FDA Response to Question 6:

Yes. An open-label study design is acceptable. However, only patients and investigator should be unblinded, and the clinical data provided to the Sponsor during the study should be blinded with respect to treatment assignment, in order to preserve the integrity of the study.

Question 7 - Proposed PFS endpoint

The proposed clinical study will evaluate PFS as the first primary endpoint. Estimated PFS in the trastuzumab-treated arm is 4 months, and MacroGenics predicts a benefit of 2 months for a hazard ratio (HR) of 0.667. Does FDA agree that, in this population, a benefit in PFS alone of 2 months as determined by an independent, blinded central radiology review may support regulatory approval?

FDA Response to Question 7:

In general, a substantial improvement in PFS that is clinically meaningful and statistically persuasive, and has an acceptable risk-benefit profile may be considered for approval. We remind you that a statistically significant difference in PFS may not necessarily demonstrate a clinically meaningful difference. Also, see response to Question # 1.

Question 8 - Proposed OS endpoint

Does FDA agree that an OS improvement of 4 months is a clinically meaningful benefit in this patient population? Would the FDA consider an improvement of less than 4 months clinically meaningful?

FDA Response to Question 8:

See response to Question # 1. If you redefine the patient population, this could be a review issue as many factors including toxicity and the potential for a changing HER2+ treatment paradigm will come into play in the overall benefit/risk analysis.

2.1 STATISTICS

Question 9 - Trial size/power

The proposed Phase 3 study will test PFS and OS as sequential primary endpoints. The size of the study is based on the assumption that OS in this population of patients treated with trastuzumab plus chemotherapy is 12 months and that the margetuximab plus chemotherapy arm will provide an additional 4 months of benefit (HR=0.75). Does FDA agree with the proposed statistical approach of using an alpha of 0.05 for both PFS and OS, with power set to 90% for PFS and 80% for OS?

FDA Response to Question 9:

The proposed approach of alpha use and power are acceptable. Also, see response to Question # 1.

Question 10 - BLA package

Does FDA agree that a combined clinical safety database of approximately 300 patients exposed to margetuximab for a median of 6 months, either alone or in combination with chemotherapy, is appropriately sized to support a regulatory submission for margetuximab, considering the intended population?

FDA Response to Question 10:
Probably yes. However, this will be a review issue.

2.2 SEALD

Question 11 - Patient reported outcomes as a secondary endpoint

Does FDA have any comments on MacroGenics' plan to include Patient Reported Outcomes (PRO) as a secondary endpoint in the proposed Phase 3 margetuximab study? In particular, does FDA have any comments on the proposed instrument(s) for collecting PRO data?

FDA Response to Question 11:
In principle we agree that the PRO instruments can be used to measure important safety concerns if those concerns represent symptoms or signs that are best captured from the patient perspective. However, we have the following comments for you:

Study Design Issues:

- **We are concerned about the potential for bias in PRO assessments of symptoms when patients and clinicians are aware of treatment assignment. Therefore, with respect to any PRO claim, the open-label nature of this clinical study will be a significant limitation that will need to be overcome by a large magnitude of effect in a carefully defined concept(s) of interest documented in the setting of strict adherence to trial conduct including limiting the amount of missing data and adherence to defined procedures for obtaining PRO data on each patient at the time of early withdrawal from the clinical trial.**

- **It is unclear why the secondary endpoints are separated into "Secondary" and "Other Secondary" categories. We note that you do not intend to conduct multiplicity adjustment of the "other secondary endpoints" which includes the PRO-related endpoint. If you are considering submitting a labeling claim, we suggest that you consider multiplicity adjustment for the secondary endpoints for which you intend to make a claim.**

- **You have not provided the entry-level criteria for the severity of symptoms in patients who will be enrolled in the Phase 3 trial. We suggest that you provide specific entry-level criteria and we recommend that symptoms of the enrolled patients be of moderate severity to demonstrate a clinically meaningful change.**

- **You have not provided details of evaluation of patients with missing data. We encourage pre-specified procedures in the clinical trial protocol to avoid missing data as well as pre-specified procedures for obtaining data on each patient at the time of early withdrawal from the clinical trial.**

PRO Assessment:

- **You have proposed the following 9 items to measure the HRQoL under the breast cancer-related Physical & Emotional Domains: lack of energy, pain, feel ill, short of breath, meeting the needs of family, fatigue, bone pain, and sleep disturbance and worry about condition worsening) for use as secondary endpoint:**

    - **The proposed items cover a broad range of concepts some of which are distal to the impact of treatment (e.g., feel ill, meeting the needs of family and sleep disturbances). Such items when used for a total score introduce a degree of variability that may make interpretation of the proposed endpoint difficult. We suggest that you focus on core symptoms that may be most common in and relevant to patients with breast cancer.**

    - **We agree that pain is an important concept to assess in the proposed context of use. However, we believe that pain and bone pain should not be assessed separately as patients may not be able to make a distinction between the two types of pain. Therefore, we suggest that only severity of pain should be evaluated.**

    - **The terms lack of energy and fatigue measure a similar concept and may be indistinguishable to patients. While fatigue is an important symptom in oncology, the concept "fatigue" is difficult to adequately measure as it is a multidimensional concept with physical, cognitive and emotional components.**

      We suggest that "fatigue" be replaced with "tiredness" The rationale is that the word "tiredness" does not imply all the of the dimensions of fatigue and may, therefore, be appropriate for labeling using a single item if adequately measured in the context of adequate and well-controlled trials.

- **You have indicated that for content validity and other measurement properties, you will be relying on the published literature. We suggest that in addition to relying on the published literature, you also establish content validity in patients with breast cancer who are enrolled in your clinical trials, and explore and evaluate measurement properties of the proposed instruments in your Phase 2 studies.**

- **You have proposed a 7-day recall period. PRO instruments that call for patients to rely on memory, especially if they must recall over a long period of time, compare their current state with an earlier period, or average their response over a period of time may not be optimal, because responses are likely to be influenced by the patient's state at the time of recall. For these reasons, items with short recall periods or items that ask patients to describe their current or recent state are usually preferable. We generally recommend that severity of symptoms be assessed daily (i.e. every 24 hours).**

- **Since you have proposed a multinational trial, we suggest that you should also consider language translation and cultural adaptation for NFBSI-16.**

- **While not a requirement, we also suggest that you consider developing an e-diary with reminder functions to improve compliance and minimize missing data.**

MacroGenics response – January 29, 2015
Regarding FDA's response to Question #11 (SEALD), MacroGenics would like to thank the Agency for their thoughtful comments on MG's plan to utilize PRO instruments in the proposed Phase 3 study. Given the FDA's feedback, further discussion and planning are warranted. With that said, MG has decided to reevaluate the QOL tool to be used, and may use a different instrument, to be described at the time of protocol submission or in a subsequent amendment.

2.3 REGULATORY

Question 12 - Intention to request waiver of the pediatric assessment requirement

Does FDA have any comments on MacroGenics' intention to request a full waiver of the pediatric assessment requirement for the proposed Phase 3 trial with margetuximab?

Per Section 505B(a)(4)(A)(i) of the Pediatric Research Equity Act of 2003, a full waiver of the requirement to submit a pediatric assessment for a drug or biological product may be granted if it is found that "necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed)."

FDA Response to Question 12:
Please review PREA REQUIREMENTS section below.

Question 13 -Additional feedback

Does FDA have additional input on the draft clinical study protocol?

FDA Response to Question 13:

1. **HER2 positive status should be defined by ASCO/CAP guidelines.**
2. **A substantial effort should be made to confirm any clinical progression with histology or imaging. Only events of confirmed clinical progression should be considered for the primary PFS analysis.**
3. **Please revise the PFS censoring rules following the FDA "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" available at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf.**
4. **Please be aware that based on your proposed protocol, analyses on the secondary endpoints would be considered as conclusive only if both PFS and OS analyses are statistically significant. Otherwise, these analyses would be considered as descriptive in nature.**
5. **The proposed analysis population for ORR and response duration is not acceptable. ORR should be calculated among patients with measurable disease at baseline. Patients with measurable disease at baseline but without a post-baseline tumor**

assessment should be considered as non-responders. Response duration should be calculated only for responders (with confirmed complete response or partial response). In addition, response duration should be removed from the Hochberg step-up procedure since it is calculated for the responder subgroup only and should not be compared by a formal statistical test.

2.4 NON-CLINICAL

Question 14 – Non-clinical chronic toxicology study

Per FDA's previous request, does the Agency agree with the proposed design of the 13-week nonclinical chronic toxicology study?

FDA Response to Question 14:

Yes, based on the information provided in your meeting briefing package, the design of your planned 13-week repeat-dose toxicology study in Cynomolgus monkeys appears appropriate to support continued clinical development of margetuximab and a future BLA submission. Please note that the final acceptance of the data generated from this study to support approval of a BLA for margetuximab will be determined following our review of the complete study report included in your submission.

Question 15 – Non-clinical reproductive and developmental toxicology

Does FDA agree that (b) (4)

is an acceptable alternative to conducting reproductive and developmental studies in monkeys?

FDA Response to Question 15:

(b) (4)

We recommend that you request our written response to this question in a subsequent submission to your IND. In this submission, provide a more detailed scientific assessment of margetuximab's developmental and reproductive toxicology that may not include studies of margetuximab in pregnant animals to support a BLA submission for the treatment of patients with advanced cancer. This subsequent IND submission should include a more detailed review of the scientific approaches, techniques and results described in the relevant cited articles and include copies of any specific literature reports used to support the reproductive toxicology assessment. (b) (4)

Following our review of this detailed assessment, we will provide you with our response as

to whether reproductive and developmental toxicology studies with margetuximab are needed to support a future BLA submission.

Meeting Discussion:
The FDA reiterated to undergo a scientific review of the potential embryo fetal toxicity and submit this information as a written response only meeting request, Type C. The agency will respond and provide feedback on this information. The FDA also reiterated that the sponsor (b) (4)

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors

regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

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

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

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.

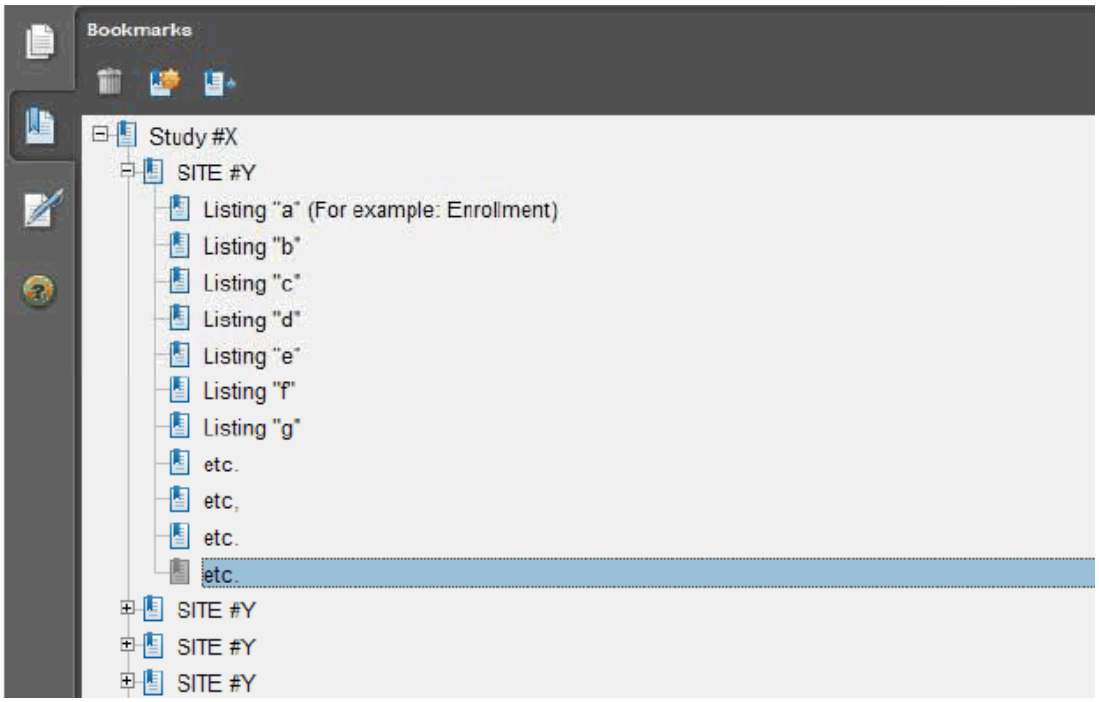
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

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 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. 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.

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

/s/

JEANNETTE L O'DONNELL
02/05/2015

PATRICIA CORTAZAR
02/05/2015