

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210498Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND113850

MEETING MINUTES

Array BioPharma Inc.
Attention: Christine Guertin, MS
Director, Regulatory Affairs
125 Cambridge Park Drive, Suite 301
Cambridge, MA 02140

Dear Ms. Guertin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for encorafenib (LGX818) and binimetinib (MEK162)

We also refer to your e-mail of February 20, 2016 containing responses to our preliminary comments sent on February 15, 2017 and requesting a change of the meeting from face-to-face to telecon, and the telecon between representatives of your firm and the FDA on February 21, 2017. The purpose of the meeting was to reach agreement with the Agency on the content and presentations of data for the NDAs to support the use of encorafenib in combination with binimetinib and binimetinib in combination with encorafenib in patients with BRAF V600 mutation-positive melanoma.

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

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

{See appended electronic signature page}

Steven Kinsley, Ph.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA CMC Only

Meeting Date and Time: February 21, 2017 1:00:00 PM
Meeting Location: Teleconference

Application Number: 113850
Product Name: LGX818, encorafenib (ARRY-438162, MEK162, binimetinib)
Indication: Treatment of patients with unresectable or metastatic melanoma harboring BRAF V600 mutations.
Sponsor/Applicant Name: Array BioPharma Inc.

Meeting Chair: Anamitro Banerjee
Meeting Recorder: Steven Kinsley

FDA ATTENDEES

Anamitro Banerjee, Ph.D.	Acting Branch Chief, Office of New Drug Products
Xing Wang, Ph.D.	Drug Product Reviewer, Office of New Drug Products
Charles Jewell, Ph.D.	Drug Substance Reviewer, Office of New Drug Products
Parnali Chatterjee, Ph.D.	Biopharm Reviewer, Office of New Drug Products
Okpo Eradiri, Ph.D.	Biopharm Team Leader, Office of New Drug Products
Derek Smith, Ph.D.	Acting Branch Chief, Office of Process and Facilities
Rahki Shah, Ph.D.	Acting Branch Chief, Office of Process and Facilities
Raanan (Ron) Bloom, Ph.D.	Environmental Assessment
Steven Kinsley, Ph.D.	Regulatory Business Process Manager
Idara Udoh	Regulatory Project Manager
Norma Griffin	Regulatory Project Manager
Patricia Keegan	Director, Division of Oncology Products II

SPONSOR ATTENDEES

Brad Barnett	Senior Director, Supply Chain and Manufacturing
Kevin Litwiler, PhD	Senior Director, Clinical Pharmacology
Christine Guertin, MS	Director, Regulatory Affairs
(b) (4)	Consultant (b) (4)
	Consultant
	Consultant
	Consultant
	(b) (4)

1.0 BACKGROUND

Encorafenib (LGX818) is a small molecule kinase inhibitor with activity against mutant BRAF kinase, a member of the RAF/MEK/ERK pathway, which plays a role in controlling several key cellular functions including growth and proliferation. Binimetinib (MEK162) is a MEK 1 and MEK 2 inhibitor. According to the meeting package, the chemistry, manufacturing, and controls for the binimetinib 15 mg tablets have been submitted in NDA (b) (4). The type 9 NDA seeking a proposed indication cited above will cross-reference the CMC information in NDA (b) (4).

On December 9, 2016, Array submitted a pre-NDA, CMC only, meeting request to reach agreement with the FDA on the content and presentations of data for the NDAs to reach agreement between Array and the FDA on the content and presentations of chemistry, manufacturing, and control data for encorafenib to support the filing of the planned NDAs for encorafenib for the proposed indications cited below. The meeting was granted on December 21, 2016 and was held on February 21, 2017, as a telecom at the request of Array. The meeting briefing document was received on January 23, 2017.

FDA sent Preliminary Comments to Array BioPharma Inc. on February 15, 2017.

2.0 DISCUSSION

DRUG SUBSTANCE

Question 1.

Does the Agency agree that release data from batches of (b) (4) (b) (4) drug substance process validation is sufficient to qualify (b) (4) as a commercial manufacturing site for drug substance (b) (4) ?

FDA Response to Question 1:

No. (b) (4) (b) (4)

Array Response:

Array acknowledges FDA's request for additional information relating to the manufacture (b) (4) The requested information will be provided in the initial NDA submission.

Discussion of Question 1:

There was no discussion of question 1.

Question 2.

Does the Agency agree that release data from a minimum of one pilot scale batch of drug substance (b) (4) is sufficient to qualify (b) (4) as a commercial manufacturing site (b) (4)

FDA Response to question 2:

No.

Array Response:

Array acknowledges FDA's recommendations regarding qualification of (b) (4) as a drug substance manufacturer. Information supporting the change will be submitted as a post-approval supplement.

Discussion of Question 2:

There was no discussion of question 2.

Question 3.

Does the Agency agree that the proposed test attributes and analytical methodology in the draft specification are adequate to confirm the quality of the commercial drug substance?

FDA Response to question 3:

The proposed test attributes appear to be adequate. Array's specified limits appear reasonable based on data in the meeting package, but FDA will assess the acceptability of these limits based on assessment of the data provided in the NDA.

Array Response:

Array acknowledges FDA's feedback and understands that a final determination on acceptability of specification limits will be a review issue.

Discussion of Question 3:

There was no discussion of question 3.

Question 4a.

Does the agency agree that the dissolution method is an adequate performance test (b) (4) ?

FDA Response to question 4a:

FDA agrees with Array's approach that the dissolution method may be used (b) (4)

However, please note that FDA cannot fully evaluate the proposed dissolution method under an IND meeting. Therefore, Array may provide the development and validation report for Array's proposed dissolution method under an amendment to Array's IND and indicate in the cover letter that Array is requesting FDA feedback/comments on its acceptability. Alternatively, Array may include the method development and validation reports in the future NDA.

Include in the dissolution method development report, detailed description of the (b) (4)

(b) (4) dissolution test. In addition, FDA recommends that Array demonstrate similarity (*f*2) or difference (*f*1) between the dissolution profiles (b) (4)

in the drug product using a suitable statistical test (*f*2, multivariate analysis, etc.).

FDA has the following general comments for the information that should be provided in Array's NDA regarding the development of the dissolution method and setting of the dissolution acceptance criteria of the proposed product:

1. **Dissolution Test:** Include the dissolution method development report supporting the selection of the proposed test. This report should include the following information:
 - a. Solubility data for the drug substance as a function of pH range;
 - b. A detailed description of the dissolution method being proposed for the evaluation of the product and the developmental parameters (*i.e.*, selection of the equipment/apparatus, dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.). If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. If possible, the dissolution profile should be

- complete and cover at least (b) (4) % of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. FDA recommends use of at least twelve discrete dosage units per testing variable;
- c. Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for Array's product. The dissolution data should be reported as the cumulative drug release with time; and
 - d. Include the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.). In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant manufacturing variables (e.g. drug substance particle size, solid state, etc.). In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent;
 - e. A list of critical material attributes (CMA) and critical process parameters (CPP) affecting;
 - f. **Data Presentation:** In the dissolution method development report, present detailed experimental data as follows:
 - Include individual vessel data as much as possible in the narrative portion of the report, particularly regarding investigation of selection of equipment, media, agitation speed, etc.
 - In addition to the mean dissolution data presented in graphical and tabular formats in the dissolution development report, submit all individual vessel dissolution data for the clinical and registration/stability batches in “.xpt” format.
 - Batch release and stability dissolution data should be presented graphically; the plot(s) of individual vessel data for the clinical and stability batches should include data at release, time zero stability time point, and over the duration of stability testing under long-term storage conditions.
2. **Dissolution Acceptance Criteria:** Provide the complete dissolution profile data (e.g. 10, 20, and 30 minutes; 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24 hours) from the clinical and stability registration batches supporting the selection of the dissolution acceptance criteria (i.e., specification-sampling time points and specification values). For the setting of the drug dissolution acceptance criteria, the following points should be considered:
- a. The in vitro dissolution specifications should encompass the timeframe over which at least (b) (4) % of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution is occurring.
 - b. Data from the lots used in the clinical trials and primary stability studies must be used.

- c. In general, the selection of the dissolution acceptance criteria ranges is based on mean target value $\pm 10\%$ and NLT ^{(b) (4)}% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved In Vitro-In Vivo Correlation (IVIVC) model.
- d. The dissolution acceptance criteria should be set in a way to ensure consistent performance from lot-to-lot and these criteria should not allow the release of any lots with dissolution profiles outside those that were tested clinically.

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA stage. However, acceptability of the proposed dissolution acceptance criteria for Array's product will be made during the NDA review process based on the totality of the provided data.

Array Response:

Array acknowledges FDA's agreement regarding Array's approach to using dissolution

*^{(b) (4)}
We further acknowledge that a final determination of acceptability will be a review issue. Additional information will be provided in the NDA.*

Discussion of Question 4a:

There was no discussion of question 4a.

Question 4b.

Does the Agency agree that the evaluation of pivotal clinical and primary stability batches

^{(b) (4)} is sufficient to confirm ^{(b) (4)}

the proposed long term storage condition and therefore ^{(b) (4)} testing in the drug product specification is not necessary?

FDA Response to question 4b:

No. FDA does not agree.

*^{(b) (4)}
^{(b) (4)}*

Array Response:

Array acknowledges FDA's observation of the limitations (b) (4)

(b) (4)

Array will provide additional data in the initial NDA submission.

Discussion of Question 4b:

There was no discussion of question 4b.

Question 5.

Does the Agency agree that the proposed test attributes and analytical methodology included in the draft drug product specification are adequate to confirm the quality of the commercial drug product?

FDA Response to question 5:

No, FDA does not agree.

(b) (4)

(b) (4)

Array Response:

Array acknowledges FDA's recommendations regarding the adequacy of the drug product specification. A revised specification will be provided in the initial NDA submission.

Discussion of Question 5:

There was no discussion of question 5.

Question 6.

Does the Agency agree that primary stability data obtained with three batches of 75 mg capsules, 90 count in (b) (4) HDPE bottles, is adequate for determination of the initial shelf life of an (b) (4) count commercial presentation of those capsules in the same bottle?

FDA Response to question 6:

Per ICH Q1A (R2), stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label). Put (b) (4)

on long term and accelerated stability studies and submit at least 6 months accelerated stability data in the original NDA submission. Demonstrate the stability conditions (b) (4)

(b) (4)

(b) (4) Compare the stability data (b) (4) if similar stability trends are achieved. The primary stability data of 75 mg capsules 90 count in (b) (4) HDPE bottles can be submitted as supporting data. The final determination will be made during NDA review.

Array Response:

Array acknowledges FDA's recommendations regarding the data required (b) (4) Array will take the Agency's feedback into consideration when presenting a proposed commercial package in the initial NDA submission.

Discussion of Question 6:

There was no discussion of question 6.

ENVIRONMENTAL ASSESSMENT

Question 7.

Does the Agency agree with the conclusion that encorafenib qualifies for Categorical Exclusion from an Environmental Assessment?

FDA Response to question 7:

No. Insufficient information is provided in the Meeting Briefing Document to make this determination at this time. (b) (4)

Array Response:

Array acknowledges FDA's requirement for additional information (b) (4) Supporting data will be provided in Module 2 of the initial NDA submission and will be cross-referenced in the request for Categorical Exclusion.

Discussion of Question 7:

The request for categorical exclusion under 21 CFR 25.31(b) should be included in Module 1.12.14 along with the data supporting the request. Cross reference can be made to Pharm Tox studies summarized in Module 2.4.

NDA SUBMISSION STRUCTURE

Question 8.

Does the Agency agree that the binimetinib CMC information in NDA (b) (4) can be incorporated by cross-reference in the proposed NDA?

FDA Response to question 8:

Refer to our preliminary response to the question 14 in the meeting dated February 06, 2017. Cross-referencing the CMC information would be acceptable. We would however recommend that you include the complete CMC information of binimetinib in the new NDA.

Array Response:

Array acknowledges FDA's feedback regarding cross-referencing the CMC information in NDA (b) (4)

Discussion of Question 8:

To facilitate the review process and document any updates to the CMC content of the new NDA, the FDA encourages Array to include the complete CMC information on binimetinib in the submission of the new NDA.

Post Meeting Comments:

Highlight changes or updates to the CMC information for binimetinib in the proposed NDA, if any, compared to the referenced NDA.

Additional Comments:

In section 6.2.2.6.1 of the Meeting Background Materials, it is mentioned that a number of analytical methods were evaluated for use in detecting and quantifying (b) (4) the drug substance (b) (4) and drug product in (b) (4) development studies. These methods included (b) (4)

- 1. Provide details and results of these studies in section 3.2.P.2 of the original NDA submission.**
- 2. Explain why (b) (4) is not used to monitor the drug substance (b) (4) in Encorafenib drug product.**

Array Response:

Array acknowledges FDA's request for additional information regarding evaluation of alternative analytical methods for detecting and quantifying (b) (4) of the drug substance (b) (4) and drug product. Additional information will be provided in the initial NDA.

Discussion:

There was no discussion.

3.0 General Comments

As stated in our December 12, 2016, communication granting the February 6, 2017, Interdisciplinary pre-NDA meeting for encorafenib 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 V. The Interdisciplinary pre-NDA meeting was held prior to the chemistry pre-submission meeting. Therefore, at this February 21, 2017, Chemistry, Manufacturing, and Controls pre-NDA 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, for encorafenib. 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.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed at the February 6, and February 21, 2017 meetings. Agreements regarding the content of the application for encorafenib were reached and documented in the meeting minutes for these meetings.

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 on the need for a REMS was held during the February 6, 2017, meeting and it was concluded that based on information currently available, FDA does not believe that a REMS will be necessary for encorafenib. FDA will make a final determination for the need for a REMS during the review of Array’s application for encorafenib.
- 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 for Array’s application for encorafenib.

In addition, we note that a multi-discipline pre-submission meeting was held on February 6, 2017. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

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.				

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types:

NDA, ANDA, BLA and Master Files must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to applicants 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), applicants must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

There were no handouts or attachments.

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

/s/

STEVEN A KINSLEY
02/27/2017

ANAMITRO BANERJEE
02/27/2017



IND 113850

MEETING MINUTES

Array BioPharma Inc.
Christine Guertin, MS, RAC
Director, Regulatory Affairs
125 Cambridge Park Drive, Suite 301
Cambridge, MA 02140

Dear Ms. Guertin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for encorafenib (LGX818) and binimetinib (MEK162).

We also refer to the meeting between representatives of your firm and the FDA on February 6, 2017. The purpose of the meeting was to reach agreement with the Agency on the content and presentations of data for the planned New Drug Applications (NDAs) for encorafenib and binimetinib:

“Encorafenib is indicated for use in combination with binimetinib for the treatment of patients with BRAF V600 mutation-positive melanoma as determined by an FDA-approved test”; and

“Binimetinib is indicated for use in combination with encorafenib for the treatment of patients with BRAF V600 mutation-positive melanoma as determined by an FDA-approved test.”

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 me at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: February 6, 2017, from 1:00 PM to 2:30 PM, EST
Meeting Location: 10903 New Hampshire Avenue, White Oak Building 22,
Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: IND 113850
Product Name: encorafenib (LGX818) and binimetinib (MEK162)

Indication: Encorafenib is indicated for use in combination with binimetinib for the treatment of patients with BRAF V600 mutation-positive melanoma as determined by an FDA-approved test

Binimetinib is indicated for use in combination with encorafenib for the treatment of patients with BRAF V600 mutation-positive melanoma as determined by an FDA-approved test

Sponsor/Applicant Name: Array BioPharma, Inc.

Meeting Chair: Dr. Marc Theoret
Meeting Recorder: Anuja Patel

FDA ATTENDEES

Patricia Keegan, Director, Division of Oncology Products 2 (DOP 2), OHOP
Marc Theoret, Clinical Team Leader, DOP 2, OHOP
Dow-Chung Chi, Clinical Reviewer, DOP 2, OHOP
Diana Bradford, Clinical Reviewer, DOP 2, OHOP
Sundee Agarwal, Clinical Reviewer, DOP 1, OHOP
Whitney Helms, Toxicology Team Leader, DHOT/OHOP
M.A. Goheer, Toxicology Reviewer, DOP 2, OHOP
Jiang Liu, Clinical Pharmacology Reviewer, OCP
Brian Furmanski, Clinical Pharmacology Reviewer, OCP
Lisa Rodriguez, Statistical Team Leader, OB/DBV
Jonathon Vallejo, Statistical Reviewer, OB/DBV
Anuja Patel, Regulatory Health Project Manager, DOP 2, OHOP
Melanie Pierce, Chief, Project Management Staff, DOP 2, OHOP

Kelie Reece, Regulatory Project Manager, DOP 2, OHOP Nataliya Fesenko, Regulatory Project Manager, DOP 2, OHOP Caryl Giuliano, Scientific Reviewer, OIR/DMGP/MGB
Mei-Yean Chen, Risk Management Analyst, OSE/DRISK

SPONSOR ATTENDEES

Renae Chavira, M.S., Pharmacologist, Clinical Sciences
Ashwin Gollerkeri, M.D., Vice President, Clinical Sciences
Christine Guertin, M.S., Director, Regulatory Affairs
Patrice Lee, Ph.D., Vice President, Pharmacology and Toxicology
Michael Pickard, Ph.D., Senior Director, Biostatistics
Victor Sandor, M.D., C.M, FRCPC, Chief Medical Officer
Margaret Vargo, M.S., Vice President, Regulatory Affairs
Lance Wollenberg, Ph.D., Senior Clinical Pharmacologist

(b) (4)

BACKGROUND

The objective of the pre-NDA meeting to be held on February 6, 2017, is to obtain agreement between Array and the FDA on the content and presentations of data to support the filing of the planned NDAs for encorafenib for the proposed indications cited below. FDA notes that NDA (b) (4) for binimetinib, which is seeking an indication (b) (4) is under FDA review.

As this meeting is also a pre-submission meeting for two new molecular entities, the forthcoming applications will be subject to “the Program” under PDUFA V. Therefore, the purpose of this meeting is also to reach agreement between Array and the FDA on the content of complete applications, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions.

The pre-meeting package received on January 9, 2017, states that encorafenib will be supplied as 75 mg capsules for oral administration, with a proposed recommended dose of 450 mg orally once daily (QD) until disease progression or development of unacceptable toxicity. Binimetinib will be supplied as 15 mg tablets for oral administration, with a proposed recommended dose of 45 mg twice daily (BID) until disease progression or development of unacceptable toxicity.

FDA sent a courtesy copy of the Preliminary Comments to Array BioPharma, Inc. via electronic mail (e-mail) on February 3, 2017, followed with an official duplicate copy through postal mail.

Array's Proposed Indications

Array seeks approval for the following two indications under two separate NDA submissions:

- Encorafenib is indicated for use in combination with binimetinib for the treatment of patients with BRAF V600 mutation-positive melanoma as determined by an FDA-approved test.
- Binimetinib is indicated for use in combination with encorafenib for the treatment of patients with BRAF V600 mutation-positive melanoma as determined by an FDA-approved test.

Regulatory History

- On April 25, 2013, preliminary responses were provided to Novartis for the April 29, 2013, Type B, End of Phase 2 (EOP2) meeting. The purpose of the meeting was to discuss Novartis' proposed trial, Study CMEK162B2301, entitled, "A Phase III randomized, 3-arm, partially blinded, placebo controlled, multicenter, study of the Combination of LGX818 plus MEK162 compared with vemurafenib, and of LGX818 compared with vemurafenib for the treatment of patients with unresectable stage IIIB, IIIC or Stage IV melanoma with BRAF V600 mutation." As presented in the meeting package, the proposed dose of encorafenib in the single-agent and combination arms were the same. In these draft responses:
 - FDA agreed that progression-free survival (PFS) was an acceptable primary endpoint for the proposed trial. FDA further stated that this endpoint may support a request for regular approval provided that a statistically significant, robust and clinically meaningful effect on PFS that is large in magnitude is observed.
 - FDA noted that a companion diagnostic test would be required for approval of encorafenib and recommended that Novartis stratify patients based on BRAF V600 mutation type (i.e., V600E vs. V600K).
 - FDA did not object to the proposed statistical analysis methods for independent comparisons of both the LGX818/MEK162 combination versus vemurafenib and LGX818 versus vemurafenib, but stated that whether the results of the trial would support a regulatory filing, however, would depend on the magnitude of the benefit observed and the results of the benefit-risk analysis. In response to Novartis' statement that "the contribution of MEK162 in the Combination will also be estimated" FDA noted that the Bayesian analysis for estimating the contribution of MEK162 to the combination of LGX818 plus MEK162 would be considered exploratory.
 - FDA recommended that the primary analyses of PFS and OS be conducted at a pre-specified number of events; that the O'Brien-Fleming method be used for alpha adjustment for interim analysis of overall survival (OS); and that given the proposal to ignore or group strata, the primary analysis should be unstratified.
 - FDA strongly recommended that Novartis submit a Pre-Submission to CDRH to discuss the analytical validation necessary to support a PMA approval for the companion diagnostic test.

- On Friday, April 26, 2013, Novartis sent an electronic communication (e-mail) providing: 1) responses to FDA’s comments, 2) new questions based on FDA’s responses to Novartis’ Questions 5a and 5m and a request that FDA provide written responses to these questions, 3) “late-breaking” information, and 4) stated that the meeting scheduled for Monday, April 29, 2013, would be cancelled unless FDA requested clarification of the late-breaking information. FDA did not request clarification of the late-breaking information and the meeting was cancelled.
- On June 14, 2013, a new clinical protocol for Study CMEK162B2301 was submitted to IND 113850; a revised protocol (amendment 1) was submitted October 25, 2013.
- On October 22, 2013, FDA issued an Advice/Information Request letter, which included the following advice:
 - “Please be advised that you will need to demonstrate the relative contribution of each investigational product to the effect of the combination in an NDA submission seeking initial approval of two previously unapproved investigational products for use in combination. Data that is limited to clinical outcomes evaluating only LGX818 and MEK162 as single agents would not be sufficient to demonstrate the contribution of each component of the combination. Please refer to the FDA Guidance for Industry “Co-development of Two or More Unmarketed Investigational Drugs for Use in Combination.”
 - “Please update the statistical section of the protocol and any other affected sections of the protocol to include BRAF V600 mutation subtype (i.e., V600E vs. V600K) as a stratification factor in the planned efficacy analyses as stated in Section 4.1.”
- On January 29, 2014, Novartis submitted Amendment #2 for Protocol CMEK162B2301. Protocol modifications in Amendment #2 included:
 - Addition of prior first-line immunotherapy (yes versus no) and removal of BRAF mutation status (V600E vs. V600K) as stratification variables for randomization.
 - Proposal to assess the treatment effects by BRAF mutation status to be investigated as a covariate in the multivariate Cox-model and in a sub-group analysis if the primary endpoints are found to be significant.
- On March 4, 2014, FDA issued an Advice/Information Request letter; the majority of the comments were previously conveyed in the October 22, 2013, Advice/Information Request letter but not addressed in the modifications to Protocol CMEK162B2301 (Amendment 2). In this letter, FDA advised:
 - That the proposed analysis assessing “The contribution of MEK162 to LGX818 in the combination arm will be estimated using the double Bayesian criteria” was exploratory.
 - To modify the protocol to include specific recommendations for ophthalmologic safety monitoring and request for dose modifications based on retinal pigmented epithelial detachment (RPED) events.
 - To modify the protocol to include BRAF mutation subtype (V600E versus V600K) as a stratification variable.
 - That the statement on page 139 of the revised protocol “Based on a blinded data review, if there are too few patients/events for a given stratum, strata might be grouped for the analysis. Further details will be provided in the analysis plan” was not acceptable.

- That the protocol should use the O'Brien-Fleming boundary method to allocate alpha for the OS analyses.
- That the protocol be modified to specify a statistical procedure controlling the overall false positive rate at a level of two-sided 0.05 for the secondary endpoints of OS and ORR.
- On February 6, 2014, Novartis submitted a meeting request to discuss their proposed changes to the ongoing trial, Protocol CMEK162B2301. The meeting package was submitted on March 11, 2014, and the Type C meeting was scheduled for April 9, 2014. The proposed additional changes to the study design of Protocol CMEK162B2301 as summarized in the March 11, 2014, meeting briefing package were:
 - A change from co-primary endpoints to a single primary endpoint, comparing PFS in the encorafenib plus binimetinib arm with the vemurafenib arm; the previous co-primary endpoint is now a key secondary endpoint (comparison of PFS in the encorafenib arm with the vemurafenib arm).
 - A reduction in the sample size from 900 to 510 patients.
 - A change in the event-driven analysis of the primary endpoint and in the event-driven analysis of the key secondary endpoint as follows:
 - The final analysis of the primary endpoint will be conducted after 87 events in order to detect a significant improvement in PFS for the encorafenib plus binimetinib arm over the vemurafenib arm with 90% power at one-sided alpha level of 0.025.
 - The final analysis of the key secondary endpoint will be conducted after 195 events in order to detect a significant improvement in PFS in the encorafenib arm compared with the vemurafenib arm at a hazard ratio of 0.75, with 80% power at one-sided alpha of 0.025.
 - The testing strategy was modified to a completely hierarchical sequential approach in the order of primary endpoint (PFS in encorafenib plus binimetinib arm vs. vemurafenib arm), key secondary endpoint (PFS in encorafenib arm vs. vemurafenib arm), OS in encorafenib plus binimetinib arm vs. vemurafenib arm, and OS in encorafenib arm vs. vemurafenib arm.
- On March 24, 2014, Novartis submitted their responses to FDA's March 4, 2014, letter. Novartis stated that a revised protocol would be provided after feedback was received to their questions from this meeting (Type C Teleconference scheduled on April 9, 2014).
- On April 2, 2014, FDA issued an Information Request Letter stating that the meeting briefing package for the April 9, 2014, teleconference contained insufficient information on the study design in Protocol CMEK162B2301 and requested submission of the statistical analysis plan (SAP) for Protocol CMEK162B2301. On April 3, 2014, Novartis submitted SAP (Version Final 1.0), which had not been updated to reflect proposed changes for discussion at the April 9, 2014, meeting.

- On April 9, 2014, a Type C teleconference was held between representatives of FDA and Novartis, to discuss the proposed changes to the ongoing Phase 3 Study CMEK162B2301. Although a number of substantive changes were proposed, the bulk of the meeting was spent discussing FDA's statements that the trial design, which employs a higher dose of encorafenib in the combination arm than the single-agent arm, would not allow an adequate assessment of the contribution of binimetinib treatment effect in the combination, that the proposal to present results from the primary efficacy analysis and immature results from the key secondary analysis without overall survival information would not provide sufficient information for filing an NDA, and that the proposed Bayesian analysis was not acceptable to assess the treatment effects of the combination. Novartis stated that the dose of encorafenib could not be increased for reasons of unacceptable toxicity; FDA agreed to review this information but did not agree with the Bayesian analysis.
- On July 23, 2014, a Type C teleconference was held between representatives of FDA and Novartis, to discuss the ongoing going study, CMEK162B2301 and to obtain feedback on the encorafenib dosing rationale and the proposed modifications to the analysis plan. Novartis proposed the parallel arms with the Recommended Phase II dose of encorafenib at 300 mg daily as a single agent and 450 mg daily in combination with binimetinib 45 mg twice a day. FDA reiterated the need for Novartis to demonstrate the relative contribution of each investigational product to the effect of the combination and that the proposed Bayesian analysis for estimating the contribution would be considered exploratory. Further the FDA stated that an application in which substantial evidence of effectiveness has not been demonstrated would not be fileable. FDA recommended that Novartis add a treatment arm consisting of encorafenib 300 mg daily in combination with binimetinib 45 mg twice daily and that analysis used to establish the contribution of binimetinib be a comparison between the encorafenib single-agent arm and the newly proposed arm.
- On November 20, 2014, Novartis submitted an amended protocol CMEK162B2301, Version 3, to modify the trial to a two-part design intended to assess the contribution of binimetinib to the effect of the combination. The second part of the trial randomized (3:1) patients to receive encorafenib 300 mg daily plus binimetinib 45 mg twice daily or single-agent encorafenib 300 mg daily. In a February 18, 2015, Advice letter, FDA stated that based on separate randomizations of patients in the single-agent encorafenib arm (Part 1 and Part 2) the encorafenib 300 mg plus binimetinib 45 mg arm (Part 2 only), there may be some imbalance in important patient characteristics with potential introduction of bias; furthermore, FDA stated that the interpretation of analyses comparing the encorafenib 300 mg plus binimetinib 45 mg arm to the single-agent encorafenib arm will depend on the results of the trial.
- On March 2, 2015, Novartis stated that Array BioPharma, Inc. (Array) regained worldwide rights to encorafenib and binimetinib from Novartis.
- On September 15, 2015, Novartis transferred sponsorship of IND 113850, and all rights and responsibilities related to the IND application to Array.

- On January 22, 2016, Array submitted a Type C, Written Responses Only meeting request to reach agreement on the clinical data plan, including the presentation of efficacy data and the pooling and presentation of clinical safety data, to support a planned NDA for encorafenib for use in combination with binimetinib for the treatment of patients with BRAF V600 mutation-positive melanoma. FDA issued final written responses on April 7, 2016.
- On February 12, 2016, Array submitted a Type C, Written Responses Only meeting request to reach agreement with the Agency on the clinical pharmacology program and the presentation of clinical pharmacology data to support a planned NDA for encorafenib, for use in combination with binimetinib for the treatment of patients with BRAF V600 mutation-positive melanoma. Final Written responses issued on April 26, 2016. FDA issued an Advice letter on July 19, 2016, in response to Array's June 9, 2016, amendment containing a request for clarification to the April 26, 2016 written response.
- On November 21, 2016, Array and FDA held an informal teleconference in response to a November 15, 2016, e-mail communication from Array requesting a meeting to discuss recent DMC recommendations to modify Part 2 of Study CMEK162B2301 and to determine whether the data are sufficient to support the encorafenib and binimetinib NDA filings. FDA stated the position that a higher dose of encorafenib in the combination arm as compared to the encorafenib single-agent arm confounds the assessment of the contribution of binimetinib to the effect of the combination.
- On November 23, 2016, Array submitted a pre NDA (clinical) meeting request to discuss and reach agreement on the content and presentations of data for the NDAs to support the use of encorafenib in combination with binimetinib and binimetinib in combination with encorafenib in patients with BRAF V600 mutation-positive melanoma. The meeting was granted on December 12, 2016. The pre meeting package was received on January 9, 2017.
- On December 9, 2016, Array submitted a pre-NDA, CMC only, meeting request to reach agreement with the FDA on the content and presentations of data for the NDAs to support the use of encorafenib in combination with binimetinib and binimetinib in combination with encorafenib in patient with BRAF V600 mutation-positive melanoma. The meeting was granted on December 21, 2016 and is scheduled to be held on February 21, 2017.
- On January 19, 2017, FDA sent an Advice letter in response to the December 23, 2016 amendment, containing the background material presented during the November 21, 2016, teleconference.

Chemistry, Manufacturing and Control (CMC)

Encorafenib (LGX818) is a small molecule kinase inhibitor with activity against mutant BRAF kinase, a member of the RAF/MEK/ERK pathway, which plays a role in controlling several key cellular functions including growth and proliferation. Agreement on the content of the CMC information an NDA for encorafenib for the proposed indication will be reached at the CMC only meeting to be held on February 21, 2017.

Binimetinib (MEK162) is a MEK 1 and MEK 2 inhibitor. According to the meeting package, the chemistry, manufacturing, and controls for the binimetinib 15 mg tablets have been submitted in NDA (b) (4). The type 9 NDA seeking a proposed indication cited above will cross-reference the CMC information in NDA (b) (4).

Nonclinical

To support the proposed NDA for encorafenib, Array plans to submit GLP-compliant single and repeat dose (28-day and 3-month) toxicity studies in rats and monkeys, genotoxicity studies (Ames and micronucleus), and reproductive teratology studies (rat and rabbit) as well as primary pharmacology, safety pharmacology (CV telemetry in monkey, hERG, neurobehavioral and respiratory in rats) for encorafenib.

Array plans to cross-reference to non-clinical pharmacology and toxicology information in NDA (b) (4) for the planned Type 9 NDA for binimetinib for the proposed indication. In addition, Array plans to submit in vitro and in vivo pharmacology data supporting the activity and rationale for binimetinib, when administered in combination with encorafenib, in the planned Type 9 NDA for binimetinib.

Clinical Pharmacology

Exposure-Response Assessment for Efficacy

The Meeting Briefing Document did not include results of Exposure-Response Assessment, but states that the exposure-response analyses for encorafenib will be conducted utilizing a population pharmacokinetic approach using the data from Study CMEK162B2301. Cox-proportional hazard regressions for PFS and OS (at a point when a formal OS analysis is conducted at approximately 232 events) will be derived based on exposure metrics of encorafenib (i.e., AUC_{ss} , C_{max} , and C_{min}) from the monotherapy encorafenib arm. A model will be then developed by simultaneously modeling the monotherapy and combo-therapy arms to evaluate the joint effect of binimetinib and encorafenib exposure on PFS.

Binimetinib exposure-efficacy analyses were conducted for model predicted exposure metrics ($C_{max,ss}$, $AUC_{tau,ss}$ and $C_{min,ss}$) and PFS, OS, and ORR in a dataset pooling information across Studies CMEK162A2301, CMEK162X2201, ARRAY-162-111 and CMEK162X1101; this pooled dataset comprises 266 patients. In the pre-meeting package, Array states that Binimetinib exposure-PFS analysis shows significant relationships with model predicted $AUC_{tau,ss}$ and $C_{max,ss}$, indicating the hazard for progression decreased with binimetinib exposure (CP16-001).

Clinical

In the premeeting package, Array proposes to present the following efficacy data from two trials in the NDAs for encorafenib and binimetinib to support the proposed indications:

- CMEK162B2301 (Part 1) and
- CLGX818X2109 (Part 1, Group A patients).

Because of differences in study designs, Array proposes not to pool the efficacy results across the two trials.

Array plans to provide safety data for seven individual clinical studies (Table 1) in the planned NDAs for binimetinib and for encorafenib. In addition, the NDAs will contain datasets pooling data across multiple studies.

- The “Broad Combination Safety Pool” will consist of safety data obtained in 433 patients who received at least one dose of planned treatment with binimetinib 45 mg twice daily administered concurrently with encorafenib at doses of 300, 400, 450, or 600 mg QD in Studies CMEK162B2301; CLGX818X2109, and CMEK162X2110.
- The Restricted Combination Safety Pool will consist of safety data from 274 patients with metastatic melanoma who received at least one dose of planned treatment with encorafenib 450 mg po once daily and binimetinib 45 mg po twice daily in Studies CMEK162B2301, CLGX818X2109, and CMEK162X2110.
- In addition, two pooled datasets will provide safety information in patients who received encorafenib as a single agent at 300 mg QD (Studies CMEK162B2301, CLGX818X2102, and CLGX818X2101) and patients who received binimetinib as a single agent at 45 mg BID (Studies CMEK162A2301 and CMEK162X2201).

Table 1. Clinical Studies Included in the Integrated Summary of Safety and Integrated Summary of Effectiveness

(Source: Array’s January 9, 2017 pre Meeting Background document)

Clinical Study	Study Design/Patient Population	Integrated Summary of Safety	Integrated Summary of Effectiveness
Encorafenib plus binimetinib			
CMEK162B2301	COLUMBUS: A 2-part Phase 3 randomized, open label, multicenter study of encorafenib plus binimetinib versus vemurafenib and LGX818 monotherapy in patients with unresectable or metastatic <i>BRAF</i> V600 mutant melanoma		Part 1 patients
CLGX818X2109	LOGIC 2: A Phase 2, multi-center, open-label study of sequential encorafenib/binimetinib combination followed by a rational combination with targeted agents after progression, to overcome resistance in adult patients with locally advanced or metastatic <i>BRAF</i> V600 melanoma	Pooled	Part 1 Group A patients ^a
CMEK162X2110	A Phase 1b/2, multicenter, open-label, dose escalation study of encorafenib in combination with binimetinib in adult patients with <i>BRAF</i> V600 - dependent advanced solid tumors		Not included
Encorafenib monotherapy			
CMEK162B2301	COLUMBUS: A 2-part Phase 3 randomized, open label, multicenter study of encorafenib plus binimetinib versus vemurafenib and encorafenib monotherapy in patients with unresectable or metastatic <i>BRAF</i> V600 mutant melanoma	Pooled	Part 1 patients

CLGX818X2102	LOGIC: A Phase 2, multi-center, open-label study of single-agent encorafenib followed by a rational combination with targeted agents after progression on encorafenib, to overcome resistance in adult patients with locally advanced or metastatic <i>BRAF</i> V600 melanoma		Not included
CLGX818X2101	A Phase 1, multicenter, open-label, dose-escalation study of oral encorafenib in adult patients with locally advanced or metastatic <i>BRAF</i> mutant melanoma		Not included
Binimetinib monotherapy			
CMEK162A2301	A randomized open-label multicenter Phase 3 study in patients with advanced unresectable or metastatic <i>NRAS</i> mutation-positive melanoma	Pooled	Not included
CMEK162X2201	A Phase 2 open-label study in patients with advanced unresectable or metastatic <i>BRAF</i> or <i>NRAS</i> mutation-positive melanoma		Not included ^b

^aPatients naïve to selective BRAF and MEK inhibitors

^bThe CSR for Study CMEK162X2201 will be referenced in the Summary of Clinical Efficacy and the Integrated Summary of Effectiveness for efficacy data, where relevant, to demonstrate the contribution of encorafenib to the combination.

The datasets pooled safety datasets and the safety datasets for the Columbus, Logic, and CMEK162X2110 trials will be provided in SDTM/ADaM, whereas the datasets for the remaining trials will be in a non-CDISC format. The data cut-off date for safety will differ from that used for the same studies submitted to NDA (b) (4). Novartis states that the SDTM datasets do not include the TD domain, but state that all variables required for analyses of PFS, OS, ORR, disposition, and adverse events will be included.

CMEK162B2301 (COLUMBUS)

CMEK162B2301 Study Design

Clinical Study CMEK162B2301, entitled, “A 2-Part, Phase III Randomized, Open Label, Multicenter Study of Encorafenib (LGX818) Plus Binimetinib (MEK162) versus Vemurafenib and Encorafenib (LGX818) Monotherapy in Patients with Unresectable or Metastatic BRAF Mutant Melanoma” is intended to serve as the primary efficacy study in support of both NDAs. The design is a two-part, multicenter, randomized, open-label trial to be conducted in approximately 900 patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as determined by the BioMerieux THxID BRAF diagnostic.

In Part 1, approximately 576 patients will be randomized in a 1:1:1 ratio to one of three treatment arms (Figure 1):

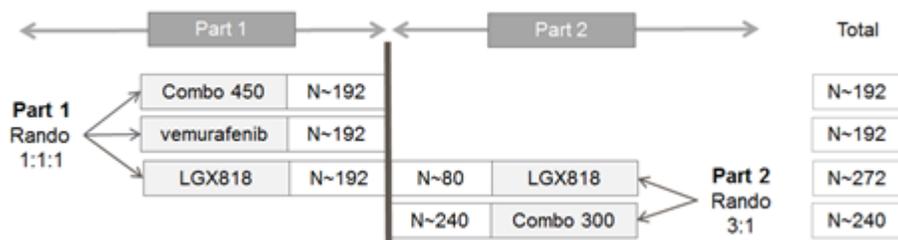
- encorafenib 450 mg once daily with binimetinib 45 mg twice daily (Combo 450) (n=192)
- encorafenib 300 mg once daily as a single agent (n=192)
- vemurafenib 960 mg twice daily (n=192)

In Part 2, approximately 320 patients will be randomized in a 3:1 ratio to one of the two treatment arms:

- encorafenib 300 mg once daily plus binimetinib 45 mg twice daily (Combo 300) (n=240)
- encorafenib 300 mg once daily as a single agent (n=80 randomized in Part 2; n=272 total with patients from Part 1)

Figure 1: Randomization Scheme, CMEK162B2301

(Source: Array's January 9, 2017 pre Meeting Background document)



The primary objective of the study is to determine whether treatment with Combo 450 (LGX818 450mg QD + MEK162 45mg BID) prolongs progression-free survival (PFS), compared with vemurafenib. Array states that key secondary objectives include determining the contribution of binimetinib to the effect of the combination based on comparisons of PFS in those randomized to the Combo 450 and encorafenib arms in Part 1 and between the Combo 300 and the encorafenib arms in Part 2.

Key eligibility criteria are: (1) histologically confirmed locally advanced unresectable or metastatic cutaneous melanoma or unknown primary melanoma (stages IIIB, IIIC, or IV); (2) presence of BRAF V600E and/or V600K mutation in tumor tissue prior to enrollment, as determined by a Sponsor-designated central laboratory(ies) using the BioMerieux THxID BRAF diagnostic; (3) treatment naïve or progressed on or after prior first-line immunotherapy for advanced or metastatic disease; (4) measurable disease per RECIST v1.1; (5) ECOG performance status (PS) 0 or 1; (6) CNS lesions must be previously treated and without evidence of progression ≥ 4 weeks and without need for corticosteroid treatment for ≥ 3 weeks; (7) left ventricular ejection fraction ≥ 50 %; and (8) no history or current evidence of retinal vein occlusion.

Randomization is stratified according to cancer stage (IIIB, IIIC, IVM1a, or IVM1b versus IV M1c), ECOG PS (0 versus 1), and prior first-line immunotherapy (yes versus no).

Tumor response is assessed by blinded independent review committee (BIRC) and by local investigators based on RECIST version 1.1 (v1.1). Tumor assessments are performed every 8 weeks for the first 24 months and then every 12 weeks thereafter. Safety assessments include routine ophthalmic examinations at screening and at every scheduled visit for patients with baseline retinal abnormalities and every four cycles for patients with no baseline retinal abnormalities. Dermatologic examinations also occur at screening and every 8 weeks. Cardiac assessments, including electrocardiogram and left ventricular heart function assessments by multigated acquisition scan or echocardiogram, occur on Cycle 1, 2, and 3, and every 12 weeks thereafter.

The primary efficacy endpoint of PFS will be determined by a central BIRC per RECIST v1.1. The primary analysis will be the comparison of the PFS distribution between the two treatment arms using a stratified log-rank test at a one-sided 2.5% cumulative level of significance; the log-rank test will be stratified by two randomization strata variables, cancer stage and ECOG PS; the two prior immunotherapy strata (yes and no) will be combined at the time of the analysis to avoid small or empty strata due to the relatively low expected prevalence of patients with prior immunotherapy (~15%).

Analyses of the key secondary PFS endpoints will use the same method as that used for the primary PFS analysis. The secondary endpoint overall survival is defined as the time from the date of randomization to the date of death due to any cause. The distribution of OS will be estimated using the Kaplan-Meier method. A stratified Cox regression analysis will be used to estimate the HR of OS, along with 95% confidence interval.

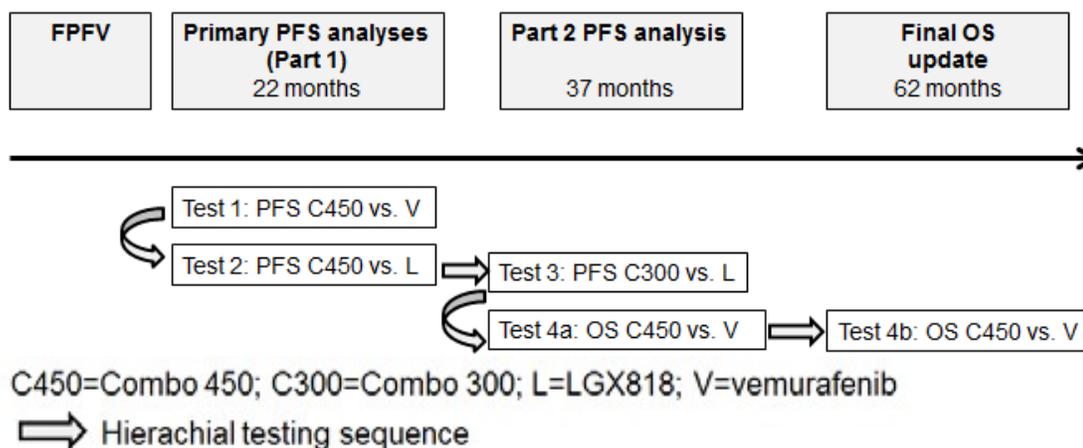
According to the statistical considerations section of Protocol CMEK162B2301 (Version 4.0), the statistical testing strategy of the primary and key secondary endpoints will follow a hierarchical, sequential approach in the order of primary endpoint (PFS comparison of encorafenib 450/binimetinib 45 and vemurafenib arms in Part 1), then the key secondary endpoints of:

1. Comparison of PFS in patients randomized to the encorafenib 450/binimetinib 45 and encorafenib 300 mg arms in Part 1 (intended to determine the contribution of binimetinib to Combo450 using PFS comparison of Combo 450 vs. encorafenib)
2. Comparison of PFS in patients randomized to the encorafenib 300/binimetinib 45 arm (Combo300) arm in Part 2 and a pooled population of patients randomized to encorafenib 300 mg arms in Parts 1 and 2 (intended to characterize this contribution more directly by using the same dose for encorafenib in each arm)
3. Comparison of overall survival in patients randomized to the Combo450 and the vemurafenib arms in Part 1 (intended to offer supportive evidence of the superiority of Combo450 vs. encorafenib using overall survival)

Figure 2 presents the testing strategy:

Figure 2. Hierarchical Testing Strategy, CMEK162B2301

(Source: Array's January 9, 2017 pre Meeting Background document)



The timing and assumptions underlying the event-driven analyses of the primary endpoint and the key secondary endpoints are as follows:

- The final analysis of the primary endpoint PFS will be conducted after 145 events in order to detect a significant improvement in PFS for the encorafenib 450/binimetinib 45 arm vs. vemurafenib arm at a hazard ratio of 0.58 (10.6 vs. 6.2)

months [per FDA Statistical Reviewer's calculation]), with 90% power at one-sided alpha level of 0.025.

- The final analysis of the Part 1 key secondary endpoint PFS will be conducted after 191 events in order to detect a significant improvement in PFS in encorafenib 450/binimetinib 45 arm vs. encorafenib arm at a hazard ratio of 0.753 (10.6 vs. 8 months), with 80% power at one-sided alpha of 0.025.
- The final analysis of the Part 2 key secondary endpoint PFS (Part 2 PFS analysis) will be conducted after 340 events in order to detect a significant improvement in PFS in encorafenib 300/binimetinib 45arm vs. encorafenib arm at a hazard ratio of 0.727 (11 vs. 8 months), with 80% power at one-sided alpha of 0.025.
- The final analysis of the secondary endpoint OS analysis will be conducted after 309 events in order to detect a significant improvement in OS in encorafenib 450/binimetinib 45arm vs. vemurafenib arm at a hazard ratio of 0.77 (22 vs. 17 months), at one-sided alpha of 0.025. One interim analysis of OS may be performed at the time of the "Part 2 PFS analysis". An α -spending function using a Gamma function with parameter 1 (as implemented in EAST 5.4) will be used. If performed, the O'Brien-Fleming boundaries will be used to adjust the final alpha based on the actual number of deaths.

Topline Results for Part 1 of Trial CMEK162B2301

At the time of data cutoff (May 19, 2016), the median duration of exposure to planned study treatment was 51.2 weeks (range, 0.4 to 116.0 weeks) in the Combo450 arm, 31.4 weeks (range, 0.1 to 113 weeks) in the encorafenib arm, and 27.1 weeks (range, 0.9 to 121.6 weeks) in the vemurafenib arm. The median duration of potential follow up for PFS per BIRC was 16.7 months for the Combo 450 arm, 16.6 months for the encorafenib arm, and 14.4 months for the vemurafenib arm.

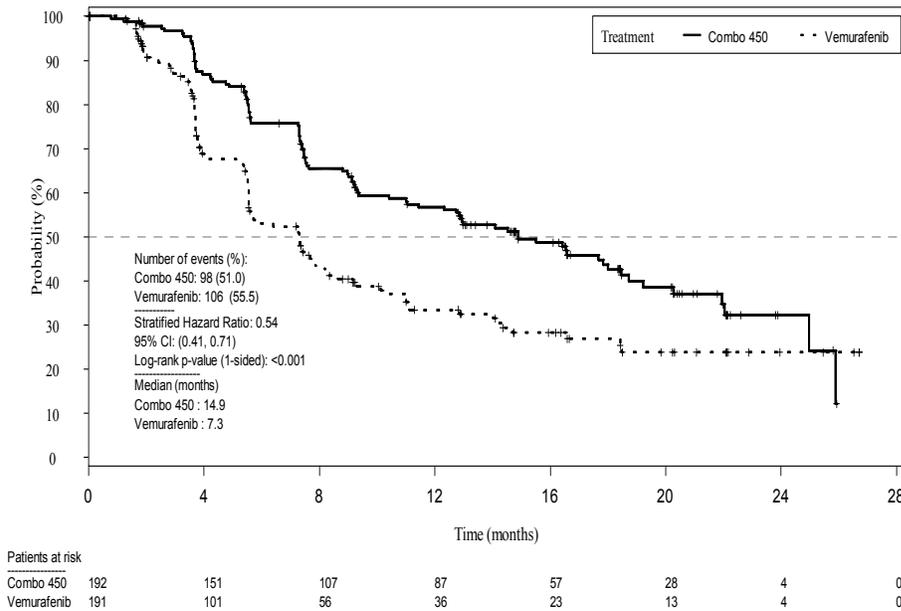
The demographics and disease characteristics for Part 1 in patients randomized to the Combo450, encorafenib, and vemurafenib arms were, respectively: median age of 57, 54, and 56 years; 60%, 56%, and 58% male; 94%, 90%, and 87% Caucasian; 71%, 72%, and 73% ECOG PS of 0; 64%, 62%, and 65% M1c disease; and 29%, 24%, and 27% elevated LDH.

Efficacy

Efficacy analyses are based on the Full Analysis Set, which consists of all randomized patients.

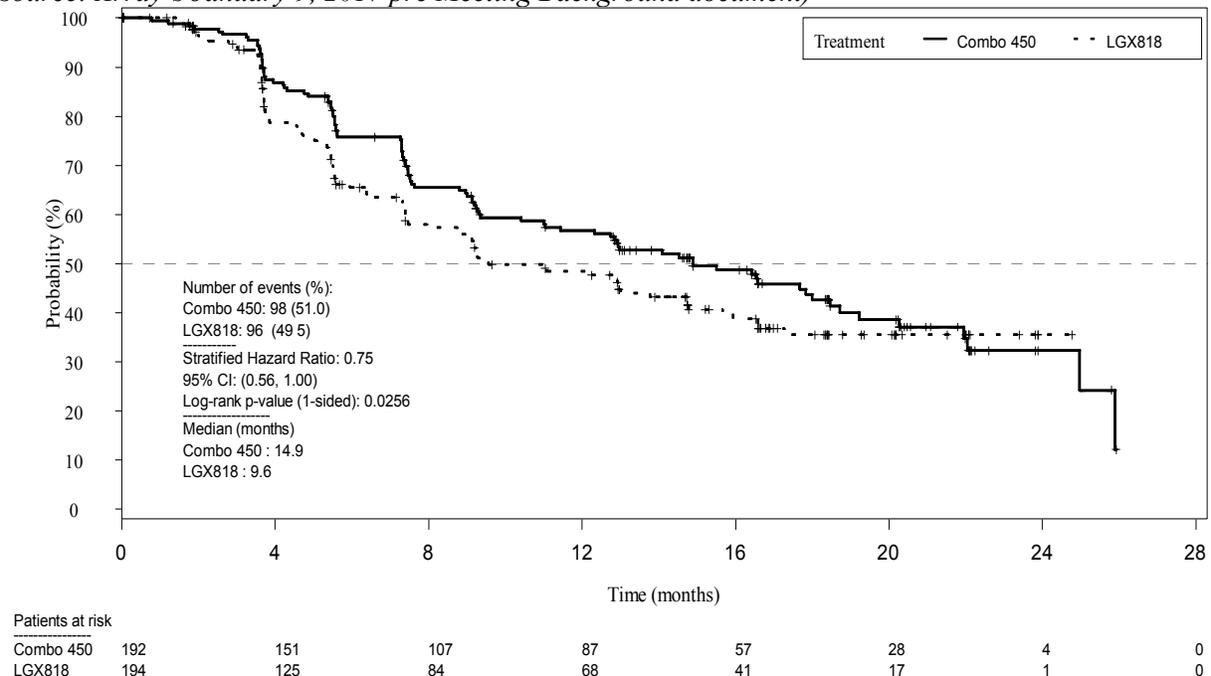
Study CMEK162B2301 met its primary endpoint with demonstration of an improvement in BIRC-assessed PFS per RECIST v1.1 for the Combo 450 arm compared with the vemurafenib arm with a hazard ratio (HR) of 0.54 (95% confidence interval [CI] 0.41, 0.71), p of <0.001 (one-sided stratified log-rank test); the median PFS in the Combo 450 arm was 14.9 months (95% CI: 11.0, 18.5) compared to 7.3 months (95% CI: 5.6, 8.2) in the vemurafenib arm (see Figure 3).

Figure 3. Kaplan-Meier Plots of BIRC-assessed PFS, Combo 450 vs. Vemurafenib
(Source: Array's January 9, 2017 pre Meeting Background document)



The primary analysis of the first key secondary endpoint in the hierarchical testing strategy, BIRC-assessed PFS in the Combo 450 arm vs. single-agent encorafenib arm, demonstrated a HR of 0.75 (95% CI: 0.56, 1.00), $p = 0.0256$ by the one-sided, stratified log-rank test according to the threshold for significance per the protocol of $p < 0.025$; the median PFS estimates were 14.9 months (95% CI: 11.0, 18.5) and 9.6 months (95% CI: 7.5, 14.8) in the Combo 450 and encorafenib arms, respectively (see Figure 4 below).

Figure 3. Kaplan-Meier Plots of BICR-assessed PFS, Combo 450 vs. Encorafenib
(Source: Array's January 9, 2017 pre Meeting Background document)



The ORRs (confirmed) as assessed by BIRC per RECIST v1.1 were 63% (95% CI: 56, 70), 51% (95% CI: 43, 58), and 40% (95% CI: 33, 48).

The pre-specified interim analysis for Part 1 overall survival (OS) has not yet occurred. Array remains blinded to the analysis results. The results of the formal interim analysis of OS, which has been proposed to be performed after 232 OS events have occurred in the Combo 450 and vemurafenib arms, are currently projected to be available in late 2017. Array plans to provide datasets that permit FDA to conduct its own analysis of overall survival.

Safety

The median duration of exposure to study treatment in the Combo450 arm was 51.2 weeks, compared to the encorafenib arm (31.4 weeks) and vemurafenib arm (27.1 weeks). Relative dose intensity of <80% for encorafenib was 30% in the Combo450 arm and 49% in the encorafenib arm. Relative dose intensity of <80% for binimetinib was 25% in the Combo450 arm. Relative dose intensity of <80% for vemurafenib was 38% in the vemurafenib arm.

Table 2 summarizes the incidence of on-treatment deaths, serious adverse events (SAEs) and other significant AEs in Part 1 of Trial CMEK162B2301.

Table 2. Summary of Patient Deaths and Adverse Events, CMEK162B2301 (Safety Set, Part 1)

(Source: Array's January 9, 2017 pre Meeting Background document)

	Combo 450 N=192		Encorafenib N=192		Vemurafenib N=186	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
On-treatment deaths ^a	17 (8.9)	--	14 (7.3)	--	19 (10.2)	--
Adverse events	189 (98.4)	111 (57.8)	191 (99.5)	127 (66.1)	185 (99.5)	118 (63.4)
Serious adverse events	66 (34.4)	57 (29.7)	65 (33.9)	54 (28.1)	69 (37.1)	60 (32.3)
AEs leading to discontinuation	24 (12.5)	22 (11.5)	27 (14.1)	21 (10.9)	31 (16.7)	18 (9.7)
AEs requiring dose interruption and/or reduction	92 (47.9)	63 (32.8)	135 (70.3)	85 (44.3)	114 (61.3)	71 (38.2)
AEs requiring additional therapy ^b	165 (85.9)	67 (34.9)	181 (94.3)	106 (55.2)	171 (91.9)	91 (48.9)

Abbreviations: AE = adverse event; EOT = end of treatment

Categories are not mutually exclusive - patients with multiple events in the same category were counted only once in that category. Patients with events in more than 1 category were counted once in each of those categories.

^a Disease progression was the most frequently reported cause of death: 6% in the Combo 450 arm, 6% in the encorafenib arm, and 9% in the vemurafenib arm. Deaths occurring >30 days after EOT were not included.

^b Additional therapy includes all non-drug therapy and concomitant medications.

On the Combo450 arm, the most frequent (>1%) serious adverse events (AE) were pyrexia, abdominal pain, anemia, acute kidney injury, cerebral hemorrhage, general physical health deterioration, pneumonia, pulmonary embolism, and vomiting. Additionally, the most frequent (>1%) AEs leading to discontinuation were ALT increased and AST increased. Common (>20%) adverse events on the Combo 450 arm were nausea, diarrhea, vomiting, fatigue, arthralgia, blood CK increase, constipation, and headache.

DMC Recommendations for Trial CMEK162B2301

On October 15, 2016, the COLUMBUS Data Monitoring Committee (DMC) convened and reviewed unblinded data for the primary analysis of PFS (Combo450 arm vs. vemurafenib arm) and the primary analysis of Part 1 key secondary endpoint #1 (PFS in the Combo450 arm vs. encorafenib arm) and recommended that the trial be terminated and the study results disclosed to investigators and to patients on the trial.

The following is a summary of the DMC's comments and recommendations:

- The study met the primary objective in Part 1 by demonstrating that COMBO450 improves PFS compared with vemurafenib (one-sided $p < 0.001$)
- The DMC recommended to terminate the study and disclose the results to investigators and to patients on the trial
- Patients on the vemurafenib arm should be offered a combination regimen of a BRAF inhibitor and MEK inhibitor
- The DMC had no recommendations for management of patients randomized to encorafenib monotherapy as the data regarding patients on encorafenib monotherapy are currently not sufficient to justify a specific recommendation as to whether these patients should be offered the opportunity to transition to BRAF/MEK inhibitor therapy, such as by the addition of binimetinib provided by Array

In response to the DMC recommendations, Array sent a letter to the investigators summarizing the DMC recommendations, asking them to notify all patients in the study of the results in Part 1, and instructing them to specifically discuss alternative therapies that are available to patients on the vemurafenib arm.

BRAF V600E/K Companion Diagnostic Development Plan

In Study CMEK162B2301, the THxID™ BRAF assay (developed by BioMérieux) was used to identify patients with BRAF V600 mutant tumors for patient eligibility based on assay results from four central laboratory locations: (b) (4)

BRAF mutational testing using the THxID™ BRAF assay was performed according to the instructions provided in the provisional product package insert for the assay, also referred to as Instruction for Use (IFU). BioMérieux has developed the THxID™ BRAF assay for the qualitative detection of BRAF WT, V600E, or V600K mutations in DNA samples extracted from formalin-fixed paraffin-embedded (FFPE) human melanoma tissue. THxID™ BRAF assay is an in vitro diagnostic (IVD) real-time polymerase chain reaction (PCR) test on the FDA cleared ABI 7500 Fast Dx system (Thermo Fisher Scientific; Waltham, MA). The THxID™ BRAF assay obtained Premarket Approval (PMA) from the U.S. FDA on 29 May 2013 (P120014) as the companion diagnostic test for dabrafenib in melanoma patients with V600E mutation and trametinib in melanoma patients with V600E or V600K mutations.

As necessary, bioMérieux intends to submit pre-submissions to CDRH to discuss the regulatory strategy for companion diagnostic approval of the THxID™ BRAF assay for binimetinib and encorafenib in melanoma. BioMérieux intends to submit a PMA supplement for a change affecting the safety or effectiveness of the device relative to the drugs binimetinib and encorafenib.

Proposed Data to Demonstrate the Contribution of Encorafenib and Binimetinib to the Effect When Used in Combination

In the Meeting Briefing Document, Array proposes that the clinical and nonclinical data demonstrates the contribution of encorafenib and binimetinib to the combination. (Refer to Table 5 below)

Table 5. Data Available in the NDA Submissions to Support Contribution of Effect

(Source: Array's January 9, 2017 pre Meeting Background document)

Efficacy (available data)

- CMEK162B2301 (A 2-part Phase 3 randomized, open label, multicenter study of encorafenib plus binimetinib versus vemurafenib and encorafenib monotherapy in patients with unresectable or metastatic BRAF V600 mutant melanoma)
 - Part 1: PFS, ORR
- CLGX818X2109 (A phase II, multi-center, open-label study of sequential Encorafenib/binimetinib combination followed by a rational combination with targeted agents after progression, to overcome resistance in adult patients with locally advanced or metastatic BRAF V600 melanoma)
 - PFS, ORR
- CMEK162X2201 A Phase 2 open-label study in patients with advanced unresectable or metastatic BRAF or NRAS mutation-positive melanoma
 - ORR

Safety

- CMEK162B2301 Part 1

Clinical Pharmacology

- Exposure-response analysis of efficacy and safety signals of interest (CMEK162B2301 Part 1)

Nonclinical (efficacy and tolerability in BRAF-mutant melanoma models)

- Contribution of binimetinib
 - [RD-2011-50576](#) (Combining encorafenib and binimetinib2 in BRAF mutant cell lines in vitro)
 - [RD-2011-50693](#) (encorafenib in combination with binimetinib in HMEX1906 melanoma)
 - [060304-1513](#) (Efficacy of encorafenib in combination with binimetinib in A375 [BRAFV600E mutant] melanoma xenografts)
- Contribution of encorafenib
 - [A375-e330](#) (Dose dependence of MEK162-NX and MEK300-NX activities, and evaluation of CFF272-NX in the A375 human melanoma nude mouse xenograft model)
 - [RD-2011-50045 \(10P-176\)](#) (A375 [BRAFV600E] human melanoma tumor xenograft model)
 - [RD-2011-50045 \(09P-265\)](#) (Malme3M [BRAFV600E] human melanoma tumor xenograft model)
 - [RD-2011-50045 \(10P-158\)](#) (HMEX1906 [BRAFV600E] primary human melanoma tumor xenograft model [PDX])
 - [060304-1513](#) (Efficacy of encorafenib in combination with binimetinib in A375 [BRAFV600E mutant] melanoma xenografts)

Array states that while Part 2 of Study CMEK162B2301 may provide supplemental data to better understand the contribution of binimetinib to a lower dose of encorafenib and will become available post-submission (currently anticipated to be early 2018), these data may not be highly informative as 1) Part 2 will not be able to strictly achieve its stated goal of isolating the effect of binimetinib independently of encorafenib exposure due to the inherent benefit of adding binimetinib to the tolerability and resulting higher achievable dose intensity of encorafenib and 2) these data may not be highly informative for labeling where the most important information is a comparison of the combination therapy with encorafenib dosed at 450 mg versus standard vemurafenib treatment.

Array believes that the data from Part 1 provide conclusive results demonstrating that binimetinib, either directly or indirectly, contributes to the safety and efficacy of the combination and that the outcome of Part 2 will not provide information that can affect this determination. Even a lack of statistical significance for the primary outcome of Part 2 will not change the conclusion from Part 1 that binimetinib allows a higher dose of encorafenib to be given with better overall tolerability and achieves a better PFS outcome (supported by other secondary outcomes) than either encorafenib monotherapy at a dose of 300 mg or standard vemurafenib treatment.

DISCUSSION

GENERAL COMMENTS

FDA will not be able to reach agreements with Array on the contents of a complete application for an NDA for encorafenib under the PDUFA V program, because the pre-NDA meeting for discussion of quality components has not been held. We acknowledge that a separate pre-NDA meeting to discuss quality components is scheduled for February 21, 2017. During this meeting FDA and Array will need to reach agreement on the CMC information necessary to allow the NDA to be considered complete and to reach agreement on submission of late components, if any are planned.

Clinical Questions

Sponsor Background to Question 1 is provided on pages 88-93 of the meeting background document:

1. Does FDA agree that the data and their analyses as described, including data describing efficacy, safety and the contribution of each agent, would be adequate to support the filing of the NDAs for the proposed indications:
 - Encorafenib is indicated for use in combination with binimetinib for the treatment of patients with BRAF V600 mutation-positive melanoma as determined by an FDA-approved test.
 - Binimetinib is indicated for use in combination with encorafenib for the treatment of patients with BRAF V600 mutation-positive melanoma as determined by an FDA-approved test.

FDA Response sent via e-mail February 3, 2017: No, the FDA does not agree.

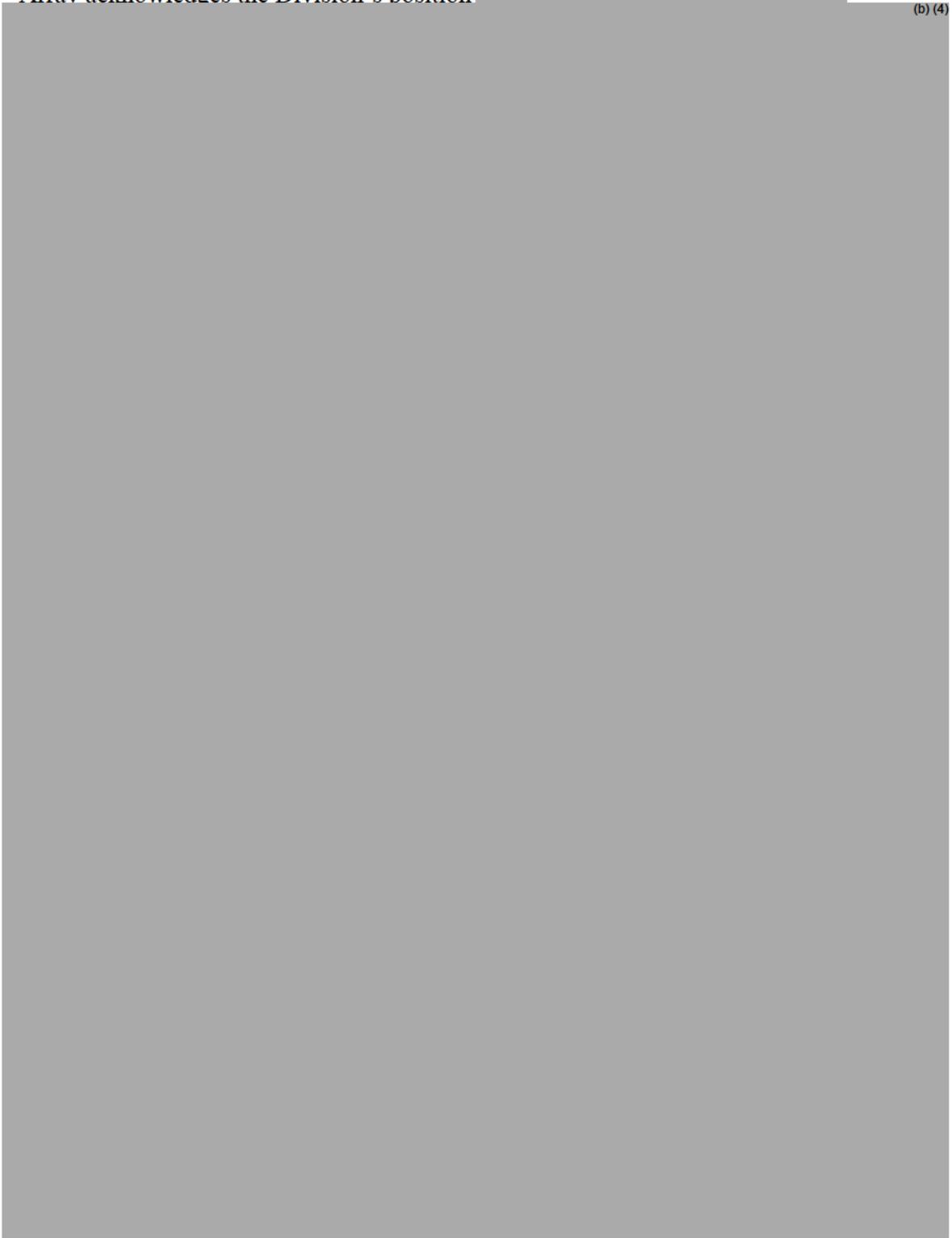
(b)
(4)

(b) (4)

Array's Response received via e-mail on February 6, 2017: Although we do not agree,
Array acknowledges the Division's position

(b) (4)

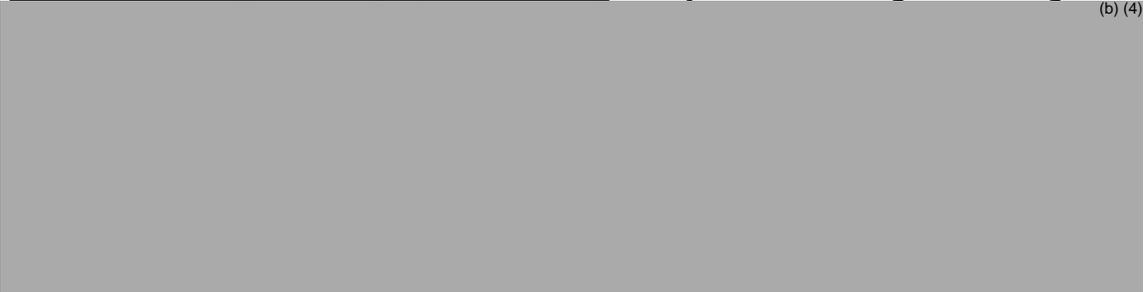
(b) (4)



Does FDA agree that the original proposal, along with the additional data described above, would be adequate to support the filing of the NDAs?

Discussion during February 6, 2017 meeting: Array clarified during the meeting that

(b) (4)



(b) (4)

FDA

acknowledged the proposed additional data to be included in the NDA may address the contribution of binimetinib. FDA stated that a final determination of the acceptability of the NDA for filing will be made upon the receipt

(b) (4)

(b) (4)



Sponsor Background to Question 2 is provided on pages 94-99 of the meeting background document:

2. The Sponsor understands that a review of data is required to determine whether changes to the dose modification schema (b) (4) is acceptable and seeks Agency guidance on whether this is feasible and if so, the types of data and analyses that may be required-

(b) (4)



Array's Response received via e-mail on February 6, 2017: Array acknowledges FDA's response. No further discussion is requested at this time, though Array may request a Type C Meeting to discuss further.

Discussion during February 6, 2017 meeting: No further discussion occurred during the meeting.

- b. Could the types of data and analyses described support such a change?

FDA Response sent via e-mail February 3, 2017: See FDA Response to Question 2a.

Array's Response received via e-mail on February 6, 2017: Array acknowledges FDA's response. No further discussion is requested at this time, though Array may request a Type C Meeting to discuss further.

Discussion during February 6, 2017 meeting: No further discussion occurred during the meeting.

- c. Are there additional specific data or analyses that might be required?

FDA Response sent via e-mail February 3, 2017: See FDA Response to Question 2a.

Array's Response received via e-mail on February 6, 2017: Array acknowledges FDA's response. No further discussion is requested at this time, though Array may request a Type C Meeting to discuss further.

Discussion during February 6, 2017 meeting: No further discussion occurred during the meeting.

Sponsor Background to Question 3 is provided on page 100 of the meeting background document:

3. Does the Agency agree that the potential risks for encorafenib in combination with binimetinib can be managed through product labeling and routine pharmacovigilance surveillance and does not require the submission of a risk management plan?

FDA Response sent via e-mail February 3, 2017: Based on the information currently available, FDA does not believe that a REMS will be necessary. FDA will make a final determination for the need for a REMS during the review of Array's application.

Array's Response received via e-mail on February 6, 2017: Array acknowledges the response. No further discussion is requested.

Discussion during February 6, 2017 meeting: No further discussion occurred during the meeting.

Sponsor Background to Question 4 is provided on page 101 of the meeting background document:

4. Does the Agency agree with the proposal to include narrative descriptions and interpretation of clinical efficacy and safety in Module 2 (Sections 2.7.3 and 2.7.4, respectively), with Module 5, Section 5.3.5.3 to include cross-references to those sections as well as appropriate integrated statistical analyses and other supportive materials?

FDA Response sent via e-mail February 3, 2017: The proposed content for Section 2.7.3 and 2.7.4, which will include a comprehensive narrative description and analysis of relevant efficacy data (~100-125 pages) and analysis of relevant safety data (~100-200 pages) with limited in-text tables and figures as appropriate, and the proposed content for the ISS and ISE in Module 5.3.5.3, which will serve as the repository for all post-text tables, figures, appendices, and datasets required to support the ISS and ISE, is adequate to support filing. Furthermore, if the level of detail required for the narrative descriptions of efficacy and safety exceed the page-limit constraints of Sections 2.7.3 and 2.7.4, respectively, FDA agrees with Array's proposal that comprehensive narrative descriptions and analysis will be developed to reside in Module 5 (Section 5.3.5.3), with more concise summaries generated to serve as the Summary of Clinical Efficacy and Summary of Clinical Efficacy, respectively.

- a. Please clarify the minimum follow-up required for inclusion of patients in the safety datasets for trials that are ongoing.

Array's Response received via e-mail on February 6, 2017: For all studies included in the integrated safety dataset, any patient receiving the relevant doses of binimetinib, encorafenib, or the combination of the two will be included in the analysis. There will be no minimum follow-up duration required to be included in the analyses. The minimum follow-up (i.e. time between last patient enrolled and data cut-off date) in CLGX818X2109 was 1.1 months. Each of the other six studies in the integrated data set (CMEK162B2301, CMEK162A2301, CMEK162X2201, CMEK162X2110, CLGX818X2102, and CLGX818X2101) had a minimum follow-up of at least 7 months.

Discussion during February 6, 2017 meeting: Refer to Discussion under Question 4c.

- b. Please clarify whether an integrated summary of safety for the Combo 300 regimen, which includes data from part 2 of the COLUMBUS trial and the study CMEK162X2110, i.e., "Safety Pool" for Combo 300, will be provided in the application.

Array's Response received via e-mail on February 6, 2017: For the initial submission, the integrated safety datasets will not include any patients receiving Combo300. There were no patients enrolled to that dose in CMEK162X2110. A full discussion of safety in patients receiving COMBO300 will be included in the file in the CSR addendum and these data will be referenced in the SCS. This data will be integrated into the safety dataset for purposes of the 4-month safety update. Please

refer to our response to Question 1 regarding the Combo300 patients in Part 2 in CMEK162B2301.

Discussion during February 6, 2017 meeting: Refer to Discussion under Question 4c.

- c. In addition, FDA requests that Array not include safety information from patients in Group B and C in study CLGX818X2109 in the pooled analysis for safety.

Array's Response received via e-mail on February 6, 2017: Currently there are two safety pools for the combination:

- A broad combination safety pool that includes all melanoma patients (naïve or exposed to prior BRAF/MEK inhibitor) receiving 45mg BID binimetinib plus encorafenib at doses between 400 and 600mg QD. Please refer to the responses to Questions 1 and 4b regarding Combo 300.
- A restricted combination safety pool that includes all BRAF/MEK naïve melanoma patients receiving 45mg BID binimetinib plus 450mg QD encorafenib.

Patients receiving encorafenib plus binimetinib during the run-in portion of Groups B and C (83 patients) are currently included in the broad combination safety pool. The median duration of exposure for these patients was 12 weeks with over a quarter of the patients receiving treatment with dual combination for at least 24 weeks. These are also not the only patients in the pooling who had progressed while on prior BRAF inhibitors. There were 19 CMEK162X2110 patients in the Phase 1b portion and 26 patients in the Phase 2 portion who had progressed while on prior BRAF inhibitor. Removing all of these patients would reduce the size of the broad combination safety pool by 128 patients. This would also remove the majority of patients in the broad combination who received doses of encorafenib other than 450mg QD in combination with binimetinib. As noted above, a restricted combination safety pool that includes only BRAF/MEK naïve melanoma patients receiving 45mg BID binimetinib plus 450mg QD encorafenib is included as a separate pool in the pooling strategy.

Does the Agency agree that the patients who progressed on prior encorafenib should still be included in the broad combination safety pool but remain excluded from the restricted combination safety pool?

Discussion during February 6, 2017 meeting: Array acknowledged FDA's responses to Questions 4a, 4b, and 4c. The following discussion encompasses discussion during the meeting of Questions 4a, 4b, and 4c.

Array clarified that for 6 of the 7 studies to be included in the broad safety pool, the minimum follow-up on study ≥ 7 months. In the planned NDA, Array agreed to provide an analysis of the time to onset of toxicity for various common toxicities, SAEs, and grades 3-4 toxicity. The NDA will not contain safety analyses in subgroups based on a minimum of duration of follow-up, but agreed to submit this information to the NDA if requested by FDA during review of the application.

Array stated that in the NDA, they would provide side by side comparisons of combination and monotherapy treatment in the restricted safety pool of 274 patients with BRAF inhibitor naïve melanoma. FDA also requested that Array provide a discussion in the SCS of differences in toxicity between those with BRAF inhibitor naïve versus BRAF experienced melanoma; Array agreed to provide this in the NDA.

Sponsor Background to Question 5 is provided on pages 102-103 of the meeting background document:

5. Does the Agency agree with the plan for submission of the 4-month safety update?

FDA Response sent via e-mail February 3, 2017: The proposed submission of a 4-month safety update is acceptable.

Array's Response received via e-mail on February 6, 2017: Array acknowledges the response. No further discussion is requested.

Discussion during February 6, 2017 meeting: No further discussion occurred during the meeting.

Sponsor Background to Question 6 is provided on page 103 of the meeting background document:

6. Does the Agency agree with the categories proposed for identifying patients for whom patient narratives and case report form pages will be provided?

FDA Response sent via e-mail February 3, 2017: The proposed criteria for submission of patient narratives (i.e., deaths, serious non-fatal adverse events, and adverse events resulting in permanent discontinuation of study drug(s)) and case report forms for all patients for whom a narrative is submitted is acceptable.

Array's Response received via e-mail on February 6, 2017: Array acknowledges the response. No further discussion is requested.

Discussion during February 6, 2017 meeting: No further discussion occurred during the meeting.

Clinical Pharmacology Questions

Sponsor Background to Questions 7 and 8 are provided on page 104 of the meeting background document:

7. Is the proposed population PK analysis adequate to evaluate the intrinsic and extrinsic factors on the PK of encorafenib?

FDA Response sent via e-mail February 3, 2017: FDA generally agrees with the proposed population PK analysis plan. Please note that using population PK analysis to assess the impact of uncontrolled concomitant medication on drug exposure is challenging because of lacking detailed dosing records of the concomitant medication (start and stop date and clock time, as well as dose and frequency). The adequacy of the analyses will be determined during the NDA review.

Array's Response received via e-mail on February 6, 2017: Array acknowledged the response. No further discussion is requested.

Discussion during February 6, 2017 meeting: No further discussion occurred during the meeting.

8. Are the planned analyses of efficacy and safety versus encorafenib and binimetinib exposures, when administered as encorafenib alone or in combination with binimetinib, adequate to support dose selection and to contribute to an assessment of relative contributions of each drug?

FDA Response sent via e-mail February 3, 2017: FDA generally agrees with the proposed exposure-response analysis plan. Please note that the application of percent relative dose intensity normalized exposure metrics may confound the exposure-response analysis for efficacy because patients who have an event (PFS or OS) later may have higher chances for dose reduction and therefore may misleadingly demonstrate a negative exposure-efficacy relationship. Also, sensitivity analysis should be conducted if dose interruption rate is high and interruption duration is long. The adequacy of the analyses to support dose selection and relative contributions of each drug will be determined during the NDA review.

Array's Response received via e-mail on February 6, 2017: Array would like to clarify the FDA's comment on exposure response. Array proposes to conduct an exposure-response analysis based on nominal exposure with sensitivity analyses of dose interruptions and interruption duration if dose interruptions are frequent and long in duration. With respect to the FDA's comment on time-averaged exposure-response analysis, Array agrees that this analysis is likely to be confounded for the reasons mentioned in the FDA response.

Does the FDA agree with forgoing the time-averaged exposure-response due to the confounding factors involved in this type of analysis, and conducting an appropriate sensitivity analysis to accompany the proposed exposure-response analysis?

Discussion during February 6, 2017 meeting: FDA generally agreed with Array's proposed exposure-response analysis plan. FDA acknowledged that the ER analysis is challenging in situations where there are high rates of dose reduction and dose interruption. FDA requested that sensitivity time to event analysis using time variant exposure as a time dependent covariant should also be conducted in lieu of the percent relative dose intensity normalized exposure if high rates of dose reduction and dose interruption have occurred. Array agreed to provide these sensitivity analyses in the NDA.

Biostatistics Questions

Sponsor Background to Question 9 is provided on pages 104-105 of the meeting background document:

9. Does the Agency agree that the proposal to delink the first interim analysis of Part 1 OS from the analysis of Part 2 of CMEK162B2301 study and conduct the analysis when 232 events are observed as anticipated in the protocol and SAP is a reasonable approach that maintains the integrity of the planned OS analysis?

FDA Response sent via e-mail February 3, 2017: Please note that no inferential claims may be made on endpoints tested beyond Test 1 because Test 2 did not achieve statistical significance in the hierarchical testing procedure. Therefore, FDA does not agree that the integrity of the planned OS analysis is maintained and any such analyses will be considered exploratory.

FDA does not object to Array conducting exploratory analyses of survival including the one that array has proposed. In addition, please provide the result of an exploratory analysis of PFS comparing the vemurafenib and encorafenib monotherapy arms.

Array's Response received via e-mail on February 6, 2017: No further discussion needed. Analyses comparing the PFS of encorafenib and vemurafenib in CMEK162B2301 will be included in the clinical study report.

Discussion during February 6, 2017 meeting: No further discussion occurred during the meeting.

Sponsor Background to Question 10 is provided on pages 105-107 of the meeting background document:

10. Does the Agency agree that the specified analyses and presentations for efficacy and safety are sufficient to support the NDA filing?

FDA Response sent via e-mail February 3, 2017: No, please refer to FDA's Responses to Question 1 and Question 9.

Array's Response received via e-mail on February 6, 2017: Please refer to our response to Q1 and Q9. Does this address the concerns of the Agency?

Discussion during February 6, 2017 meeting: FDA acknowledged the additional data to be submitted in the NDA, as discussed under Question 1. Inclusion of this additional data will modify the proposed safety and efficacy analyses to be provided in the NDA. FDA has no objection to the inclusion of additional data with the exception of any additional discussion under Question 4.

Sponsor Background to Question 11 is provided on pages 107-109 of the meeting background document:

11. Does the Agency agree that the format of the clinical datasets that will be included in the submission is sufficient to support the NDA filing?

FDA Response sent via e-mail February 3, 2017: Yes. Although Array may submit datasets using the non-CDISC format for trials initiated before the CDISC requirement date, FDA strongly recommends submission of datasets using CDISC standards. If Array chooses to submit data in an alternative format, FDA encourages Array to follow CDISC standards as much as possible. In addition, FDA encourages Array to submit a mock dataset of the clinical data for FDA to comment on the proposed format and contents.

Array's Response received via e-mail on February 6, 2017: For studies with CSR data in non-CDISC format, Array will also submit the data in SDTM format (with an associated Define file and reviewers guide) as this will be used to create the integrated safety ADaM dataset.

With regards to the mock data sets, are there specific datasets that are of concern?

Discussion during February 6, 2017 meeting: FDA stated that there were no specific datasets of concern.

Sponsor Background to Question 12 is provided on page 110 of the meeting background document:

12. Does the Agency agree with the plan for submission of SAS programs?

FDA Response sent via e-mail February 3, 2017: No. Please include in Array's submission (a) SAS programs that produced all efficacy results, (b) all raw as well as derived variables in .xpt format, (c) SAS programs by which the derived variables were produced from the raw variables, and (d) results of any interim analysis if ever performed.

Array's Response received via e-mail on February 6, 2017: All data will be submitted in .xpt format, and there were no interim analyses for CMEK162B2301. The DMC reviewed safety data at regular intervals, but they only reviewed efficacy data after the Part 1 database lock.

The submission for the BRAF melanoma indication will require a very large number of data and files and will be quite complex. In an effort to minimize the complexity, would the agency be amenable to receiving additional codes regarding specific variables/endpoints in a timely manner during the review period if questions arise?

Discussion during February 6, 2017 meeting: FDA requested the that NDA contain reviewers guides, SAS programs for primary and key secondary analyses, macros for any derived variables for primary and key secondary analyses and censoring rules for parts 1 and 2 of the COLUMBUS trial. Array confirmed that they would provide the requested information as well as additional SAS programs upon request.

Nonclinical Question

Sponsor Background to Question 13 is provided on pages 110-111 of the meeting background document:

13. Does the Agency agree that the nonclinical packages for encorafenib and for binimetinib are sufficient to support the NDA filings?

FDA Response sent via e-mail February 3, 2017: The available information appears sufficient to support the filing of an NDA. A final determination of the adequacy of the data to support approval will be made after the review of the study reports and literature at the time of the original NDA submission.

Array's Response received via e-mail on February 6, 2017: Array acknowledges the response. No further discussion is requested.

Discussion during February 6, 2017 meeting: No further discussion occurred during the meeting.

Regulatory Questions

Sponsor Background to Question 14 is provided on pages 111-112 of the meeting background document:

Module	Binimetinib NRAS Mutant Melanoma NDA (b) (4)	Binimetinib BRAF Mutant Melanoma NDA	Encorafenib BRAF Mutant Melanoma NDA
1	X	X	X
2	X ←	Cross reference to most encorafenib BRAF mutant melanoma NDA Module 2 documents; Cross reference to Binimetinib NRAS mutant melanoma QOS	X
3	X ←	Cross reference to NDA (b) (4)	X
4	X ←	Will contain binimetinib only study reports; May cross reference reports previously submitted in NDA (b) (4)	Will contain encorafenib only and binimetinib + encorafenib study reports
5	X ←	Will contain binimetinib only study reports; May cross reference reports previously submitted in NDA (b) (4)	Will contain encorafenib only and binimetinib + encorafenib study reports

X = inclusion of file and/or report leafs
→ denotes the direction of a cross reference leaf

14. Does the Agency Agree with the proposed NDA Tables of Contents and with the approach of cross-referencing as described?

FDA Response sent via e-mail February 3, 2017: The proposal to cross-reference NDA (b) (4) for CMC information and non-clinical and clinical studies containing information for binimetinib only information and the proposed Table of Contents are acceptable. However, Array should also identify all information Array will reference that is contained in an IND file, including the IND number, date of submission, and type of information being cross referenced. Finally, the NDAs should contain hyperlinks to any cross-referenced information in another file (NDA (b) (4) or an IND file).

Array’s Response received via e-mail on February 6, 2017: Array acknowledges the response. No further discussion is requested.

Discussion during February 6, 2017 meeting: No further discussion occurred during the meeting.

Sponsor Background to Questions 15 and 16 are provided on pages 112-113 of the meeting background document:

15. Does the Agency agree that providing financial disclosure for Studies CMEK162B2301, CLGX818X2109 and LGX818X2101 is sufficient to address the Agency's requirements for financial disclosure information in support of these NDAs?

FDA Response sent via e-mail February 3, 2017: The proposal to submit financial disclosures for the all investigators involved in the aforementioned studies appears to be acceptable.

Array's Response received via e-mail on February 6, 2017: Array acknowledges the response. No further discussion is requested.

Discussion during February 6, 2017 meeting: No further discussion occurred during the meeting.

16. Does the Agency agree that clinical study reports for studies CMEK162X1101, CMEK162X2201, CLGX818X2101, CLGX818X2102 and CLGX818A2101 can be submitted in legacy format?

FDA Response sent via e-mail February 3, 2017: The proposal to submit some CSRs in legacy format and some in granular format appears to be acceptable.

Array's Response received via e-mail on February 6, 2017: Array acknowledges the response. No further discussion is requested.

Discussion during February 6, 2017 meeting: No further discussion occurred during the meeting.

CDRH Regulatory Question

Sponsor Background to Question 17 is provided on pages 113-114 of the meeting background document:

17. Does the Agency agree that the timing of the planned PMA supplement submission allows for concurrent review of the PMA supplement and NDAs without impacting the timing for approval of the NDAs?

FDA Response sent via e-mail February 3, 2017: If the PMA supplement for the THxID™BRAf Assay is submitted concurrent with the NDA, CDRH will review the PMA concurrently with the NDA. It should be noted that should additional analytical validation be included in the PMA, CDRH recommends that the PMA be submitted in advance of the NDA in order for BioMerieux to have sufficient time to address any deficiencies that may arise during the course of review.

Array's Response received via e-mail on February 6, 2017: Array acknowledges the response. No further discussion is requested.

Discussion during February 6, 2017 meeting: No further discussion occurred during the meeting.

ADDITIONAL FDA COMMENTS

Clinical Pharmacology

18. In the NDA submission address polymorphisms in CYP2C19 and UGT for encorafenib metabolism. Provide justification with supporting data if Array believes that the risk of these polymorphisms on changing systemic exposure, safety and tolerability of encorafenib is low.

Array's Response received via e-mail on February 6, 2017: Array has discussed this in prior written responses with the FDA (IND 113850 SN 0781, submitted on 09 June 2016). The sponsor will include this justification and the supporting *in vitro* and *in vivo* data to support these claims in the NDA.

Discussion during February 6, 2017 meeting: FDA accepted Arrays proposal for Question 18. No further discussion occurred during the meeting.

Clinical

19. Confirm that the safety datasets will include separate variables to identify adverse events that led to dose reduction and those that led to dose interruption.

Array's Response received via e-mail on February 6, 2017: The data does not necessarily support these variables. These variables can be generated for CMEK162B2301, CMEK162A2301, and CLGX818X2109, but they would need to be carefully interpreted. In these studies, sites were allowed to select only one action taken for an adverse event, and they were instructed to select the most severe action. A hierarchy was provided, and dose interruptions were described to be more severe than dose adjustments. Based on this, an action recorded as a dose interruption may or may not have also led to a dose reduction. So a variable that flags adverse events requiring a dose reduction would underestimate the true number of dose reductions. For the other studies (CMEK162X2201, CMEK162X2110, CLGX818X2102, and CLGX818X2101), the CRFs did not separate dose interruptions from dose adjustments. The sites could only select one action which grouped these actions together. For these studies, the two requested variables cannot be included.

Array will provide an integrated exposure dataset that flags all dose reductions and all dose interruptions. Array will also include a variable in the integrated adverse event dataset that lists the action taken on each adverse event per the CRF. Does the Agency agree that this information is sufficient?

Discussion during February 6, 2017 meeting: Array clarified that the CRFs captured only the most clinically significant action taken for an adverse event (i.e., if dose reduction and subsequent termination of dosing occurred for the same event, the only action captured was termination of dosing). Array agreed to provide information on all actions taken for adverse reactions resulting in dose reduction, dose interruption, and termination of dosing in order to support proposed product labeling.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

FDA noted during the February 6, 2017, meeting that a chemistry pre-submission meeting for encorafenib is scheduled for February 21, 2017. A summary of agreements reached at that meeting will be documented in the minutes for the February 21, 2017 meeting for the encorafenib NDA.

Binimetinib NDA

- The content of a complete application was discussed. Agreements regarding the content of the application were reached during the February 6, 2017, meeting and documented in these meeting minutes.

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 on the need for a REMS was held and it was concluded that based on information currently available, FDA does not believe that a REMS will be necessary. FDA will make a final determination for the need for a REMS during the review of Array's application for binimetinib.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. Array stated their intent to submit a complete application; therefore, there are no agreements for late submission of application components.

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.

Because encorafenib and binimetinib have orphan drug designation for this indication, 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.

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.

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 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).

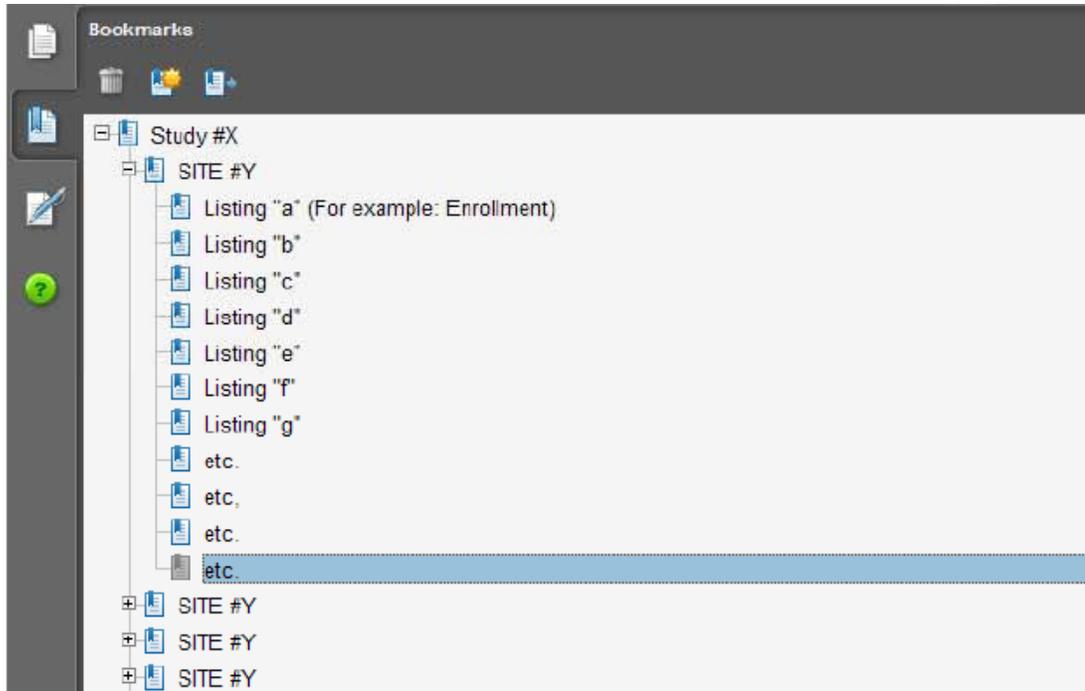
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

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

ISSUES REQUIRING FURTHER DISCUSSION

As discussed above, a chemistry, manufacturing, and controls pre-submission meeting for encorafenib is scheduled for February 21, 2017. A summary of agreements on the content of a complete application will be reached at that meeting will be documented in the minutes for the February 21, 2017 meeting for the encorafenib NDA.

ACTION ITEMS

There were no action items identified during the meeting.

ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

ANUJA PATEL
02/20/2017



IND 113850

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Jeffrey Stuart, Ph.D., RAC
Director, Drug Regulatory Affairs
One Health Plaza, Building 104
East Hanover, NJ 07936-1080

Dear Dr. Stuart:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "LGX818/MEK162."

We also refer to the meeting scheduled between representatives of your firm and the FDA on April 29, 2013. The purpose of the meeting was to seek FDA's responses on questions contained in your meeting briefing document and to obtain any additional comments on your proposed Phase 3 study, Protocol CMEK162B2301. FDA's preliminary comments were provided to you by electronic mail (e-mail) on April 25, 2013.

We also acknowledge your electronic mail (e-mail) message of April 26, 2013, in which you provided responses to FDA's draft responses, requested that the April 29, 2013 meeting be cancelled, and also requested that FDA provide written responses to new questions based on FDA's responses to Novartis' Clinical Pharmacology Questions 5a and 5m.

A copy of the official minutes, which includes FDA's draft responses issued on April 25, 2013, Novartis' responses and new questions provided on April 16, 2013, and FDA's responses to the additional questions posed in the April 26, 2013 e-mail relating to Novartis' original questions 5a and 5m, is enclosed for your information.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

If you have any questions, call me at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Anuja Patel, M.P.H.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of Phase 2/Pre-Phase 3

Meeting Date and Time: Monday, April 29, 2013
12 Noon to 1:00 P.M.

Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421

Application Number: IND 113, 850
Product Name: LGX818/MEK162
(Proposed) Indication: BRAF V600-dependent advanced solid tumors
Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation

TENTATIVE LIST OF FDA ATTENDEES

Richard Padzur, M.D., Director, Division of Oncology and Hematology Products (OHOP)
Patricia Keegan, M.D., Director, Division of Oncology Products 2 (DOP 2), OHOP
Joseph Gootenberg, M.D., Deputy Director, DOP 2, OHOP
Suzanne Demko, P.A.-C., Clinical Team Leader, DOP 2, OHOP
Maitreyee Hazarika, M.D., Clinical Reviewer, DOP 2, OHOP
Whitney Helms, Ph.D., Toxicology Team Leader, DHOT/OHOP
Sachia Khasar, Ph.D., Toxicology Reviewer, DOP 2, OHOP
Ali Al Hakim, Ph.D, Branch Chief, Medical Imaging, ONDQA
Liang Zhao, Ph.D., CMC Team Lead, DNDQA1/ONDQA
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader
Ruby Leong, Pharm.D., Clinical Pharmacology Reviewer
Stacy S. Shord, Pharm. D., Genomics and Targeted Therapy Reviewer
Rosane Charlab Orbach, Ph.D, Genomics and Targeted Therapy Acting Team Leader
Kun He, Ph.D., Statistical Team Leader, OB/DBV
Xiaoping (Janet) Jiang, Ph.D., Biometrics Reviewer, OB/DBV
Caryl Giuliano, Ph.D., CDRH, OIR, DIHD Scientific Reviewer
Donna Roscoe, Ph.D., CDRH, OIR, DIHD, IHGB Acting Branch Chief
Reena Philip, Ph.D., CDRH, OIR, DIHD Deputy Director
Elizabeth Mansfield, Ph.D, CDRH, OIR Director, Personalized Medicine
Anuja Patel, M.P.H, Regulatory Health Project Manager, DOP 2, OHOP
Monica Hughes, M.S., Chief, Project Management Staff, DOP 2, OHOP

TENTATIVE LIST OF SPONSOR ATTENDEES

David Lebwohl, M.D., Global Program Head, Novartis
Judith Klimovsky, M.D, Global Clinical Program Head, Novartis
Laure DeParseval, M.D., Senior Global Clinical Lead, Novartis
Kris Grzegorzewski, M.D., Sr. Medical Director, US Clinical Development and Medical Affairs, Novartis
Ranjana Tavorath, M.D., Executive Director, Clinical Resident Physician, Novartis
Annie St. Pierre, Ph.D., Clinical Pharmacology Fellow, Novartis
Elizabeth Molloy, Program Statistician, Novartis
Christine Granfield, Ph.D., Director Regulatory Affairs, Companion Diagnostics, Novartis
Stephan Wong Ph.D., Global Program Director, Companion Diagnostics, Novartis
Daniel Monney, Ph.D, Global Program Regulatory Director, Novartis
Jeffrey Stuart, Ph.D. Senior Associate Director, Drug Regulatory Affairs, Novartis
Shanthi Ganeshan, Ph.D., Executive Director, Global Head Early Programs, Drug Regulatory Affairs, Novartis
Howard Holden, Ph.D., Vice President Drug Regulatory Affairs, Array BioPharma

Disclaimer:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for April 29, 2013, 12 P.M. to 1:00 P.M., 10903 New Hampshire Avenue, White Oak Building 22, Silver Spring, Maryland, between Novartis Pharmaceuticals Corporation Healthcare Pharmaceuticals Incorporated (Novartis) and the Division of Oncology Products 2. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

The meeting briefing package was received March 27, 2013.

Meeting Purpose:

Novartis Pharmaceuticals Corporation plans to initiate Study CMEK162B2301 entitled, “A Phase III randomized, 3-arm, partially blinded, placebo controlled, multicenter, study of the Combination of LGX818 plus MEK162 compared with vemurafenib, and of LGX818 compared with vemurafenib for the treatment of patients with unresectable stage IIIB, IIIC or Stage IV melanoma with BRAF V600 mutation.” This trial is intended to support marketing approval of two investigational agents, LGX818 and MEK162, for LGX818 as a single agent or LGX818 in combination with MEK162 for the initial treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations.

The primary purpose of the meeting is to receive FDA’s feedback on the proposed study CMEK162B2301, and discuss the questions Novartis has proposed in their March 26, 2013, meeting briefing package.

Draft FDA comments were sent to Novartis Pharmaceuticals Corporation on April 25, 2013.

1.0 BACKGROUND

On February 22, 2013, Novartis submitted a Type B, End-of-Phase 2 meeting request to discuss the proposed Phase 3 study CMEK162B2301 to evaluate the efficacy of both LGX818 plus MEK162 in combination, and LGX818 monotherapy, as compared to vemurafenib, in patients with unresectable or metastatic melanoma with BRAF V600 mutation.

Proposed Indication

Study CMEK162B2301 is intended to be the registration study to support the proposed indication: “LGX818 (either in combination with MEK162 or as monotherapy) is indicated for the treatment of patients with unresectable or metastatic melanoma harboring BRAF V600 mutations as determined by an FDA-approved test.”

Chemistry, Manufacturing, and Controls for LGX818

The chemical name for LGX 818 is (S)-methyl (1-((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate. Novartis describes LGX818 as a highly selective ATP-competitive small molecule RAF kinase inhibitor, which suppresses the RAF/MEK/ERK pathway in tumor cells expressing BRAF V600. LGX818 is currently available as capsules for oral use in dosage strengths of (b) (4) 50 and (b) (4) mg.

Chemistry, Manufacturing, and Controls for MEK162

The chemical name for MEK162 is 5-[(4-Bromo-2-fluorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1H-benzimidazole-6-carboxamide. Novartis describes MEK162 as a potent and selective allosteric, ATP (Adenosine Tri-Phosphate) non-competitive inhibitor of MEK1/2 that is active in inhibiting pERK and growth of BRAF mutant cancer cells in the low nanomolar range. The film coated tablets are currently available at dosage strengths of 15 mg (b) (4).

Chemistry, Manufacturing, and Controls for LGX818 and MEK162 in Combination

Novartis states that LGX818 capsules will be co-administered orally with MEK162 tablets. The study drugs will be administered as a flat-fixed dose, and not by body weight or body surface area. LGX818 and MEK162 will be packaged separately.

Nonclinical

Nonclinical information for LGX818

LGX818 is a kinase inhibitor targeting RAF kinases including the BRAFV600E mutation. Novartis has completed 4-week GLP-compliant toxicology studies of LGX818 in rats and monkeys. In rats, primary LGX818-related toxicities were skin lesions, including dry, scaly, and thickened skin on the plantar surface of the feet, which histologically presented as slight to marked hyperkeratosis, squamous cell hyperplasia, and inflammatory cell infiltration. Results from the rat 4-week GLP toxicology studies at 20, 100 and 400 mg/kg/day showed that plasma exposure (AUC) after single and multiple doses of LGX818 increased approximately proportionally with the increasing dose between 20 to 400 mg/kg/day in male rats. A similar trend was observed in female rats. In general, female rats consistently showed approximately 2-fold higher exposure than male rats. After multiple dosing, there was no consistent difference in plasma exposures compared to single dose exposure in both male and female rats.

Nonclinical information for MEK162

The biological activity of MEK162 has been evaluated *in vitro* (both enzymatic and cell culture assays) and *in vivo* in mouse xenograft studies. MEK162 potently inhibits MEK1/2 in both biochemical assays using purified protein, and in cells. MEK162 has demonstrated growth inhibitory activity in a wide variety of cancer cell lines. Novartis states that in a collection of approximately 500 genetically annotated cell lines, MEK162 showed anti-proliferative activity preferentially in cells harboring activating mutations of the MAP kinase pathway (e.g. BRAF, NRAS and KRAS), and, in particular, activating mutations of BRAF and NRAS, and that *in vivo*, MEK162 has demonstrated dose dependent tumor growth inhibition in various subcutaneous tumor transplants harboring BRAF V600E mutations (HT29, COLO205, A-375) as well as activating mutations in both NRAS (Hs. 944T) and KRAS (MiaPaCa2, A549, LoVo, Calu6). These data suggest that MEK162 may provide a potential therapeutic benefit in cancer indications harboring these mutations, including melanoma. Short (28-day) and long term (6-9 month) GLP-compliant toxicology studies have been completed in both rats and monkeys. In animals, exposure (AUC) and C_{max} generally increased in a dose proportional manner. Predominant MEK-162-related toxicities consisted of various skin lesions, including exudates, erosions, inflammation and scabbing and soft tissue mineralization of numerous internal organs (in rats) and degeneration of the intestinal epithelium resulting in enteritis and inflammation (in monkeys).

Nonclinical information for LGX818 and MEK162 in Combination

The March 26, 2013, meeting briefing document states no LGX818/MEK162 combination toxicity studies have been conducted. The combination of LGX818 and MEK162 demonstrated additive or synergistic antiproliferative activity in a panel of BRAF mutant human melanoma and colorectal cell lines with no evidence of antagonism. The combination of LGX818 and

MEK162 was also tested in nude mice implanted with the HMEX1906 (BRAFFV600E) human melanoma primary xenograft model with limited toxicologic endpoints (body weight, clinical pathology and limited histopathology). In this model, single agent LGX818 and MEK162 induced tumor regression, however, the response was transient and the majority of tumors developed resistance over the course of four months of treatment. Based on the initial publications regarding RAF inhibitor resistance, which suggested that reactivation of the RAF/MEK/ERK pathway is responsible for resistance to RAF inhibitors in melanoma tumors, the combination of LGX818 and MEK162 was anticipated to prevent or delay the emergence of resistance in this study. Results confirmed that the combination prevented the emergence of resistant tumors over the four month duration of the study. Novartis believes that these data support the hypothesis that combining LGX818 and MEK162 will be efficacious in treating human melanoma. The combination of LGX818 (3 mg/kg bid) and MEK162 (10 mg/kg bid) revealed no additional toxicities compared with each agent alone except for infiltration of lymphoplasmacytic/neutrophilic cells in the periportal area of the liver. Novartis did not consider this change adverse because of the low incidence, severity and the inflammatory nature of the observation. Novartis suggests that gastrointestinal intolerance/toxicity and myelosuppression may be dose limiting in the clinical setting when these agents are combined and that rash, and decreased white blood cell production are expected toxicities which should be reversible upon cessation of drug.

Novartis states that nonclinical in vitro data indicate that main pathways of metabolism for MEK162 include glucuronidation by UGT1A and to a lesser extent oxidation by CYP1A2 and CYP2C19. The formation of the oxidative metabolite AR00426032 that accounts for less than 25% of the parent in humans was mediated mainly by CYP1A2, and with minor contribution by 2C19 and 2B6. UGT1A1 was the primary enzyme to mediate glucuronidation of MEK162, with minor involvement of UGTs 1A3, 1A4, 1A7, 1A9, and 2B7. Novartis claims that LGX818 is a weak ($IC_{50} \geq 20 \mu M$) reversible inhibitor of CYP1A2, CYP2C8, CYP2C19 and CYP2D6. LGX818 is also a UGT1A1 inhibitor with in vitro IC_{50} ranging from 4 to 7 μM , thus LGX818 is not expected to significantly affect the pharmacokinetics of MEK162 by metabolism mediated drug-drug interactions. Novartis stated that MEK162 is a BCRP substrate while LGX818 is an inhibitor of BCRP ($IC_{50} = 10-25 \mu M$). Since the concentration of LGX818 in the gut is expected to be ~0.4 mM with 50 mg dose (assuming all drug dissolved in 250 mL volume), there is a potential for increased MEK162 exposure due to BCRP-inhibition by LGX818.

Clinical

Clinical Development for LGX818

Novartis states that LGX818 has been tested as micro-emulsion (ME) and capsule (CPS) formulations in a Phase 1 dose escalation study in patients with locally advanced or metastatic melanoma or CRC, whose tumors have a mutation of the BRAF V600 gene.

The March 26, 2013, meeting briefing document states that at the cut-off date of 7 January 2013, 68 patients have been enrolled in the CLGX818X2101 study (54 in the dose escalation and 14 in the dose expansion). At the time of the cutoff, 13 of 54 (24.1%) patients were ongoing in the dose escalation phase with 4 (7.4%) discontinued due to an adverse event, and 13 of 14 (92.9%)

patients were ongoing in the dose expansion phase with none discontinued due to an AE. The MTD was determined to be 450 mg/day.

In the dose-escalation phase dose levels ranged from 50-700 mg qd (n=42) and 75-150 mg bid (n=12) and all patients were treated in the dose-expansion phase at 450 mg qd, (5 patients with metastatic CRC, 9 patients with melanoma - 1 naïve and 8 previously treated with a selective BRAF inhibitor). Novartis reported that the most common adverse events (AEs) in the dose expansion phase ($\geq 20\%$) suspected to be treatment related were dry skin, arthralgia, myalgia, nausea, decreased appetite, insomnia, hand-foot skin reaction (HFSR), vomiting, asthenia, and maculo-papular rash. The following dose-limiting toxicities occurred in the dose expansion phase grade 3 bone pain and vomiting (one patient) and grade 3 myalgia and arthralgia (one patient).

A summary of clinical studies conducted with LGX818 is provided in Table 1 of the Appendix.

Clinical Development for MEK162

Novartis states in their March 26, 2013, meeting briefing package that MEK162 (also known as ARRY-438162) is an orally bioavailable, selective and potent MEK inhibitor. Novartis believes that this compound will potentially benefit individuals with advanced cancers by inhibiting the RAS/RAF/MEK/ERK pathway. MEK162 has previously been examined by Array in the treatment of rheumatoid arthritis based on the role the RAS/RAF/MEK/ERK pathway also plays in inflammatory processes. MEK162 has been evaluated in 3 completed studies in healthy subjects (single ascending dose, multiple ascending dose, single-dose relative bioavailability and food effect) and 2 completed studies in patients with rheumatoid arthritis (a Phase 1 multiple ascending dose study and a Phase 2 study, both in combination with methotrexate).

The experience with MEK162 as a single agent in oncology patients includes 3 ongoing studies with a total of 216 patients enrolled as of January 7, 2013. These are 2 Phase 1 studies: ARRAY-162-111 in patients with solid tumors with an expansion phase in biliary and colorectal cancer, (in this study a dose range from 30 to 80 mg BID has been explored), and CMEK162X1101 in Japanese patients with solid tumors and an expansion in patients with RAS or BRAF mutations, and one Phase 2 study, CMEK162X2201, in patients with advanced melanoma in which 45 mg and 60 mg BID dose levels have been explored.

The experience with MEK162 in cancer patients in combination studies comprises 7 ongoing Phase 1 studies with a total of 216 patients enrolled as of January 7, 2013.

In single agent studies, one patient treated at a dose of 60 mg BID experienced fatal, acute liver failure assessed to be related to MEK162. In melanoma studies, frequently reported AEs suspected to be related to the study drug in single agent studies are acneiform dermatitis, diarrhea, peripheral edema, increased blood creatinine kinase, nausea, fatigue, rash and vomiting. Novartis reports that most of these adverse events were Grade 1 or 2 with less than 5% Grade 3-4 reported, with the exception of elevation of blood creatine kinase. Additional clinical significant events were central serious retinopathy (CSR)-like events and cardiac events.

A summary of clinical studies with MEK is provided in Table 2 of the Appendix

Clinical Development of LGX818 and MEK162

Novartis describes their ongoing combination clinical study CMEK162X2110 under IND 113,850. The study is a multi-center, open-label, dose finding, Phase 1b dose escalation study to estimate the MTD(s) and/or RP2D(s) for the combination of LGX818 and MEK162, followed by a Phase 2 part to assess the clinical efficacy and to further assess the safety of the combination in selected patient populations. The dose escalation is conducted in adult patients with locally advanced or metastatic melanoma, metastatic colorectal cancer (mCRC) or any other solid tumor harboring the BRAF V600E mutation, or any other BRAF V600 mutation, whose disease has progressed despite previous anti-neoplastic therapy or for whom no further effective standard therapy is available. Once MTD/RP2D has been determined, patients with BRAF V600 mutant mCRC for whom no further effective standard therapy is available will be enrolled in arm 1 of the Phase 2 part of the study. Patients with locally advanced or metastatic BRAF V600 mutant melanoma who have progressed after previous treatment with a selective BRAF inhibitor will be enrolled in arm 2. Patients with locally advanced or metastatic BRAF V600 mutant melanoma who are naïve to previous treatment with a selective BRAF inhibitor will be enrolled in arm 3. Novartis states that based on the substantial activity and good tolerability of LGX818 and LGX818+MEK162 combination in phase 1 studies LGX818X2101 and MEK162X2110, the phase 3 study will be initiated while the MEK162X2110 phase 2 study is ongoing.

As stated in the meeting briefing package, in the clinical study CMEK162X2110, patients with BRAF V600 - dependent advanced solid tumors received escalating doses of a combination of LGX818 plus MEK162. LGX818 oral doses of 50 mg, 100 mg, 200 mg, 400 mg, or 600 mg were administered once daily concurrent with twice daily doses of MEK162 45 mg given orally. The pharmacokinetics of both drugs was investigated after a single dose (Day 1) and multiple doses (Day 15) in Cycle 1. Trough samples were collected on Day 1 of each cycle from Cycle 2 to 10. As this study is on-going, all data presented are considered preliminary.

When administered with LGX818, C_{max} of MEK162 was slightly higher than what has been observed in the single agent studies, but the values were still within the variability range of what is known for MEK162. There was an increase in apparent clearance of MEK162 with increasing doses of LGX818 from 50 mg to 600 mg. Novartis states that the sample size in each cohort was limited ($n \leq 6$) and the apparent clearance could be estimated only in a few individuals per cohort. Exposure of the metabolite was low (~20% or less) compared to that of the parent drug, as observed in single agent studies.

LGX818 absorption was rapid reaching median T_{max} around 1.5 hours and then declined with a terminal elimination half-life of around 3 hours. Exposure on Day 15, as determined by C_{max} and AUC, was 30 to 70% less than compared with Day 1, likely due to auto induction of CYP3A by LGX818 (data not supplied). This effect of LGX818 on its own PK was also seen in single agent studies with LGX818. PK characteristics of LGX818 when co-administered with MEK162 were similar to those observed in the single agent study CLGX818X2101.

In the combination study (CMEK162X2110), the common AEs were nausea, diarrhea and headache. Increase in lipase, maculo-papular rash and AST/ALT increases were also seen. The MTD for the study has not yet been reached.

Patient Population To Be Studied

According to the March 26, 2013, meeting briefing package, approximately 900 adult patients, with histologically confirmed locally advanced unresectable or metastatic BRAF V600 mutant cutaneous melanoma (stage IIIB, IIIC to IV per American Joint Committee on Cancer [AJCC]) as determined by a central laboratory, with no prior systemic anti-cancer therapy (treatment-naïve) in the advanced or metastatic setting, will be randomized in this study. Novartis will permit prior systemic treatment in the adjuvant setting. Patients randomized in this study are not permitted to participate in additional parallel investigational drug or device studies. Once a patient has completed the study, they may not be re-enrolled.

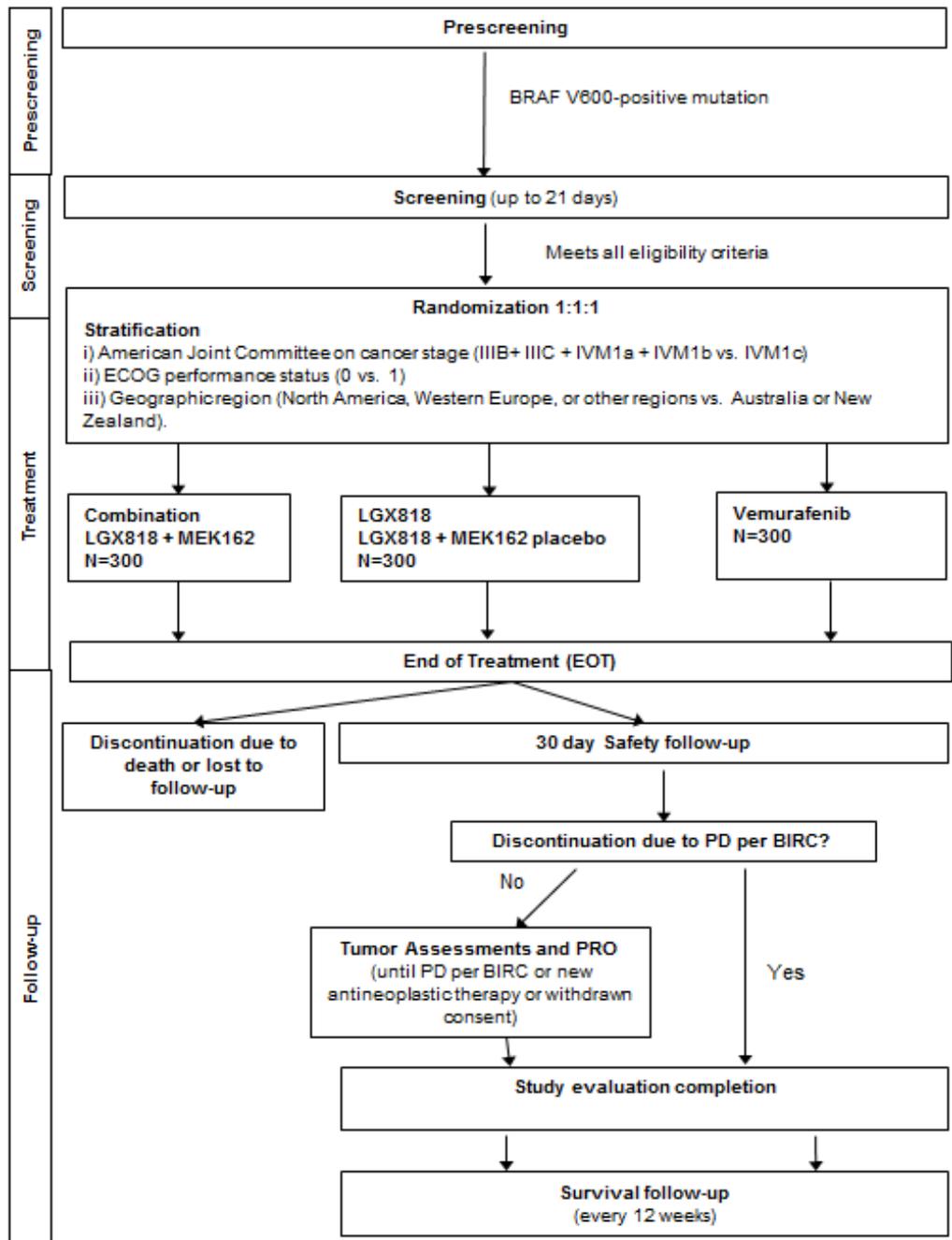
Proposed Study Design for Study CMEK162B2301

The proposed trial, CMEK162B2301, is a randomized, partially blinded, placebo-controlled, multicenter, parallel group, 3-arm trial in patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Randomization will be stratified by AJCC stage (IIIB + IIIC + IVM1a + IVM1b vs. IVM1c), ECOG performance status (0 vs. 1), and Geographic region (North America, Western Europe, or other regions vs. Australia or New Zealand). A total of 900 patients will be randomly assigned in a 1:1:1 ratio to the following 3 treatment arms:

- Experimental 1: LGX818 plus MEK162 (denoted as Combination arm)
- Experimental 2: LGX818 plus MEK162-placebo (denoted as LGX818 arm)
- Control: vemurafenib

Eligible patients will have histologically confirmed locally advanced unresectable or metastatic BRAF V600 mutant cutaneous melanoma (stage IIIB, IIIC to IV per AJCC) as determined by a central laboratory, with no prior systemic anti-cancer therapy (treatment-naïve) in the advanced or metastatic setting. Prior systemic treatment in the adjuvant setting is allowed. Patients must have evidence of at least one measurable lesion as detected by radiological or photographic methods according to RECIST version 1.1 as modified by Novartis guideline version 3.1. Novartis proposes to use an Investigational Use Only (IUO) diagnostic test that detects BRAF V600 (V600E and V600K) gene mutations to select patients eligible for this study.

The Proposed Study Design for Study CMEK162B2301 is shown in the following figure:



Patients will be assessed for efficacy (CT/MRI and physical examination with pictures if appropriate) every 8 weeks during the first 24 months (104 weeks) and every 12 weeks thereafter until progression. Safety monitoring and patient reported outcomes (PRO) for quality of life (QOL) will be assessed as per visit schedule. Response to treatment will be determined by RECIST version 1.1 as modified by Novartis into guideline version 3.1. Patients will continue

treatment with the study drug until progressive disease according to RECIST version 1.1 as determined by the Blinded Independent Review Committee (BIRC) , intolerable toxicity, withdrawal of consent to continue study treatment, death, physician decision or early termination of the study. After progression or after study treatment discontinuation, patients will continue to be followed for survival every 12 weeks until approximately 670 deaths are observed.

The primary efficacy endpoint is PFS with two planned pair-wise comparisons, LGX818 plus MEK162 versus vemurafenib and LGX818 versus vemurafenib. The final analyses for PFS in each comparison will be after 103 PFS events for the comparison of LGX818 plus MEK162 versus vemurafenib and 302 PFS events for the comparison of LGX818 versus vemurafenib. Based upon the assumption that the median PFS is 6 months in the vemurafenib arm and 12 months in the LGX818 plus MEK162 arm, a total of 103 events are needed to detect a hazard ratio of 0.5 with 90% power at a 1-sided alpha level of 0.0125. Based upon the assumption that the median PFS is 6 months in the vemurafenib arm and 9 months in the LGX818 arm, a total of 302 events are needed to detect a hazard ratio of 0.667 with 90% power at a 1-sided alpha level of 0.0125. The primary efficacy analysis will be a stratified log-rank test at a one-sided alpha of 0.0125 performed on the ITT population for each of the pairwise comparisons, i.e., the comparison of the LGX818 plus MEK162 arm vs. vemurafenib arm and the comparison of LGX818 arm vs. vemurafenib arm.

The secondary endpoint of overall survival will also be tested independently for each pairwise comparison (LGX818 plus MEK162 arm versus vemurafenib arm and LGX818 arm versus vemurafenib arm). The comparison of OS will be formally statistically tested only if the primary efficacy analyses of PFS are met. Based upon the assumption that the median OS is 13.5 months in the vemurafenib arm and 18.5 months for the LGX818 plus MEK162 arm, a total of 450 events are needed to detect a hazard ratio of 0.73 with 80% power at a one-sided alpha level of 0.0125. Based upon the assumption that the median OS is 116.5 months in the LGX818 arm, a total of 460 events will provide 39% power to detect a hazard ratio of 0.82 at a one-sided alpha level of 0.0125. Two interim analyses of OS will be performed, one at the time of the final PFS analysis and another at the time of the PFS/OS update. The three-look Lan-Demets group sequential design with Gamma function method (a separate α -spending function using a Gamma function with parameter 1) is utilized based on the actual number of deaths available for the considered comparison.

Other secondary endpoints include best overall response (BOR), overall response rate (ORR), and disease control rate (DCR). A hierarchical procedure is not proposed to adjust for multiplicity in testing the other secondary endpoints besides OS.

An additional secondary efficacy objective is to estimate the contribution of of MEK162 to the observed PFS treatment effect in in the LGX818 plus MEK162 arm by comparison to the LGX818 monotherapy arm using a Bayesian double criterion at the time of final PFS analyses, and re-estimated at the time of the PFS/OS update analysis.

Additional analyses of PFS and OS will be conducted when a total of 388 PFS events have occurred in the LGX818 plus MEK162 and LGX818 arms. Based on the protocol assumptions,

this is planned around 34 months after first patient first visit (FPFV). The added treatment effect will be considered to be clinically relevant if the estimated HR (LGX818 plus MEK162 arm versus LGX818 arm) ≤ 0.85 (corresponding to an increase in median PFS from 9 to 10.5 months) and the posterior probability (HR LGX818 plus MEK162 arm versus LGX818 arm < 1.0) $> 90\%$.

Preliminary FDA responses were emailed to Novartis on April 25, 2013. Novartis emailed their responses to FDA on April 26, 2013, stating that they wanted to cancel the meeting and receive written responses to clinical pharmacology Questions 5a and 5m. On April 29, 2013, FDA acknowledged Novartis responses and agreed to provide additional clarification to the clinical pharmacology questions via written responses. As a result, on April 29, 2013, Novartis and FDA agreed that the meeting was no longer necessary and FDA agreed to provide additional written responses to Questions 5a and 5m.

2. DISCUSSION

SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSE

1. **The proposed patient population is patients with advanced melanoma harboring a BRAF V600 mutation. Does the FDA agree with the use of a BRAF V600 test that can identify both V600E and V600K mutations for selection of patients for the proposed study?**

FDA RESPONSE:

Yes.

FDA has the following additional comments:

- a. Because a companion diagnostic BRAF V600 mutation assay will be necessary for use of the therapeutic LGX818 alone or in combination with MEK162, FDA recommends that an IDE submission be made to CDRH that includes a demonstration of analytical validity using the specimen type(s), and a pre-specified method prior to trial initiation. Please note that Novartis' test should accurately detect both BRAF V600E and V600K mutations and Novartis should provide sufficient information that your test is safe for use in your trial. CDRH strongly recommends that Novartis submit a Pre-Submission to CDRH to discuss the analytical validation necessary to support a PMA approval.
- b. FDA recommends that Novartis stratify patients in study CMEK162B2301 based on BRAF V600 mutation (i.e. V600E vs. V600K), as different BRAF V600 mutations may confer differential sensitivity to BRAF inhibition.
- c. Please refer to the following draft guidance documents on the In Vitro Companion Diagnostic Devices and the Pre-Submission Program found at:

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf>, and

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>.

NOVARTIS RESPONSE RECEIVED VIA ELECTRONIC MAIL ON APRIL 26, 2013: Novartis acknowledges FDA's comments a through c. Novartis plans to stratify by region, of which prevalence of different V600 mutations differs and could be confounded. Furthermore, there are already 3 prospective stratification factors, and additional factors would increase the chance for empty cells. Thus, Novartis will stratify at time of analysis for type of BRAF V600 mutation rather than at randomization.

- 2. PFS is the proposed primary endpoint. Does the Agency agree that PFS, as defined in the protocol synopsis, would support filing in this indication?**

FDA RESPONSE:

Yes, PFS is an acceptable primary endpoint for the proposed trial. This endpoint may support a request for regular approval provided that a statistically significant, robust and clinically meaningful effect on PFS that is large in magnitude is observed.

However, FDA strongly recommends that both radiology and clinical assessments be used to identify disease progression; whichever (clinical or radiologic tumor progression) is noted first should be used to determine the date of progression. In addition, describe the method and plan of assessment and planned analyses in detail in the protocol and SAP.

NOVARTIS RESPONSE RECEIVED VIA ELECTRONIC MAIL ON APRIL 26, 2013: Novartis acknowledges FDA's comments. Novartis confirms that there will be independent radiology and clinical assessments, and the first of whichever event will be used to determine the date of progression. This will be further clarified in the protocol and SAP.

- 3. The proposed 3 arm design allows for independent comparisons of both the LGX818/MEK162 combination versus vemurafenib and LGX818 versus vemurafenib. The contribution of MEK162 in the Combination will also be estimated. Does the agency agree that the proposed statistical approach could support a filing for LGX818 alone and/or the Combination of LGX818 & MEK162 in this indication?**

FDA RESPONSE:

Yes, FDA does not object to the proposed statistical analysis method, and the approach could be acceptable in support of a regulatory filing. Whether the results of the trial will support a regulatory filing, however, will depend on the magnitude of the benefit

observed and the results of the benefit vs. risk analysis. FDA notes that the Bayesian analysis for estimating the contribution of MEK162 to the combination of LGX818 plus MEK162 will be considered exploratory.

NOVARTIS RESPONSE RECEIVED VIA ELECTRONIC MAIL ON APRIL 26, 2013: Novartis acknowledges FDA's comments.

4. **Novartis proposes using a single radiology reader and a clinician instead of 2 radiology readers plus adjudication and a clinician for assessment of the primary endpoint. Does the agency agree?**

FDA RESPONSE:

Yes, the proposal to use a clinician is acceptable for the integrated radiology / clinician assessments. Please see also FDA response to Question 2.

NOVARTIS RESPONSE RECEIVED VIA ELECTRONIC MAIL ON APRIL 26, 2013: Novartis acknowledges FDA's comments.

5. **Does the agency agree with the proposed clinical pharmacology plan?**

FDA RESPONSE:

FDA generally agrees with the proposed clinical pharmacology plan, but has the following additional recommendations.

Revise the proposed Phase 3 trial protocol to include the following:

- a. Collect additional sparse pharmacokinetic samples pre- and post-dose after repeat doses (e.g., on day 15).

NOVARTIS RESPONSE RECEIVED VIA ELECTRONIC MAIL ON APRIL 26,

2013: In the proposed Phase 3 study, Novartis plans to collect PK samples at 5 timepoints: pre-dose samples on Day 1 of Cycles 1 to 3, and 2 post-dose samples on Cycle 1 Day 1. This schedule was based on a sampling optimization methodology using the population PK model of MEK162. Novartis acknowledges the importance of characterizing the approach to steady-state for LGX818 due to the time-dependency. In order to do this, pre- and post-dose PK samples are collected in CLGX818X2101 (single agent study in patients with melanoma) on Day 8 and Day 15, from which we will have data in approximately 30 patients.

In addition, Novartis is collecting pre-dose PK samples at every cycle and post-dose PK samples on Cycle 1 Day 1 and Cycle 1 Day 15 in CMEK162X2201 (single agent study of MEK162 in melanoma) and CMEK162X2110 (combination study with MEK162 and LGX818 in melanoma). This data will further enrich the pool of PK in this indication.

Novartis would like to avoid the extra burden of collecting additional PK samples on patients enrolled in the Phase 3 study.

FDA WRITTEN RESPONSE IN LIEU OF APRIL 29, 2013: FDA agrees with Novartis' approach with the understanding that pharmacokinetic data of LGX818 and MEK162 will be incorporated from all available trials for the final population pharmacokinetic analysis.

- b. Collect pharmacokinetic samples for measurement of MEK162 metabolite, AR00426032.

NOVARTIS RESPONSE RECEIVED VIA ELECTRONIC MAIL ON APRIL 26, 2013: Novartis acknowledges FDA's recommendation and is planning to collect PK samples for measurement of this MEK162 metabolite. The same analytical method is used for the measurement of MEK162 and AR00426032.

- c. Modify the fasted conditions to state that the study drugs should be taken at least 1 hour before or 2 hours after a meal.

NOVARTIS RESPONSE RECEIVED VIA ELECTRONIC MAIL ON APRIL 26, 2013: Novartis acknowledges FDA's recommendation and will revise the Phase 3 protocol to reflect this.

During the development of LGX818, conduct the following studies or provide justification for not conducting any specific studies:

- d. Conduct a renal impairment study based on the 2010 draft FDA Renal Impairment Guidance found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf>. This guidance states that a pharmacokinetic study should be conducted in patients with impaired renal function if a drug is primarily metabolized or secreted in bile.
- e. Conduct a drug-drug interaction study to evaluate the effect of a strong CYP3A4 inducer on the pharmacokinetics of LGX818.
- f. Conduct additional drug-drug interaction studies to evaluate the effect of LGX818 on the pharmacokinetics of sensitive CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 substrates. The inhibition potential of LGX818 may be assessed by simultaneous administration of a mixture of CYP substrates in one study (i.e., a "cocktail approach"). Alternatively, if the drug interaction study that includes a sensitive substrate of the CYP with the largest R value shows no interaction, *in vivo* evaluation of other CYPs with smaller R values will not be necessary.

- g. Conduct a drug-drug interaction study to evaluate the effect of a P-gp inhibitor on the pharmacokinetics of LGX818.
- h. Conduct a drug-drug interaction study with a gastric pH elevating agent (proton pump inhibitor, histamine receptor antagonist, or antacid) given that LGX818 exhibits pH-dependent solubility.
- i. Conduct drug-drug interaction studies to evaluate the effect of LGX818 on the pharmacokinetics of a BCRP and OATP substrate.

NOVARTIS RESPONSE RECEIVED VIA ELECTRONIC MAIL ON APRIL 26, 2013: Novartis acknowledges FDA's recommendations and will consider additional clinical pharmacology studies for LGX818 to address comments *D thru I* above. Novartis plans to approach FDA in the future to specifically discuss the clinical pharmacology strategy and data for both compounds as single agents and in combination.

- j. Conduct an *in vitro* study to determine if LGX818 is a substrate of BCRP.

NOVARTIS RESPONSE RECEIVED VIA ELECTRONIC MAIL ON APRIL 26, 2013: An *in vitro* study was conducted with Ko143, a BCRP inhibitor indicating that LGX818 is not a substrate of BCRP.

- k. Submit the proposed plan with available ECG data to evaluate the potential for LGX818 to prolong the QT interval for QT-IRT to determine the adequacy of the plan and the need for a 'TQT' study.

NOVARTIS RESPONSE RECEIVED VIA ELECTRONIC MAIL ON APRIL 26, 2013: Study CLGX818X2101 (single agent) was amended to incorporate the collection of ECGs on Day 1 and Day 15, at 0.5 hours, 2 hours, 6 hours and 24 hours post-dose. This will allow exploration of the relationship between QTc and plasma concentrations of LGX818 for patients with PK collection (a subset of patients in the dose escalation phase and approximately 20 patients in the dose expansion phase). For other patients a 2 hours (~ Cmax) post-dose ECG was added.

The plan will include analysis of delta QTc consistent with E14 ICH guidance. The results from this evaluation will be submitted to the health authorities for review prior to the first NDA and the need for a TQT study will be evaluated at that time.

In addition, FDA has the following recommendations in regard to MEK162:

- l. A renal impairment study for MEK162 with a full PK study design, instead of the proposed reduced PK study design, may be warranted depending on the results of the ADME study in humans.

NOVARTIS RESPONSE RECEIVED VIA ELECTRONIC MAIL ON APRIL 26, 2013: Novartis acknowledges FDA's recommendation.

- m. Please refer to the clinical pharmacology comments that have been provided during the EOP2 meeting for MEK162.

NOVARTIS RESPONSE RECEIVED VIA ELECTRONIC MAIL ON APRIL 26, 2013: Novartis acknowledges FDA's recommendation.

As an additional modification, there is a minor change proposed for the DDI study with LGX818 and ketoconazole. Novartis intends to conduct the study at steady-state in patients, as the safety profile of LGX818 would not allow 21 days of daily dosing in healthy volunteers. The underlying time-dependency of LGX818 oral drug clearance is likely to be auto-induction of CYP3A4-mediated metabolism (predominantly pre-systemic), in addition to possible contribution of P-gp –mediated efflux. Auto-induction is likely to result in increased contribution of CYP3A4 (and P-gp) to overall metabolism (and efflux) of LGX818 at steady-state when compared to single dose administration. Concomitant administration of LGX818 with a dual CYP3A4/P-gp inhibitor is anticipated to result in a larger increase of LGX818 exposure when the inhibitor is given after 21 days of daily LGX818 (steady-state) as compared to single dose LGX818. This strategy may be applied to other planned CP studies should we decide to conduct the study at steady-state.

Does the agency agree with this plan?

FDA WRITTEN RESPONSE IN LIEU OF APRIL 29, 2013 MEETING: FDA agrees with Novartis' plan.

Novartis proposes to use total bilirubin and ALT/AST levels as a measure of hepatic dysfunction for the hepatic impairment studies for both drugs. In vitro and preclinical in vivo data suggest that the main metabolic pathway for MEK162 is glucuronidation. Furthermore, both LGX818 and MEK162 are mainly being evaluated in patients with advanced solid tumors. A large proportion of these patients develop liver metastases with various degrees of hepatic dysfunction caused by liver involvement and/or biliary obstruction. Hepatic dysfunction in cancer patients mainly consists of abnormal biologic liver tests reflecting chronic cholestasis with elevation in the levels of bilirubin, alkaline phosphatase (ALP), and gamma glutamyl transferase (GGT) with or without abnormal levels of aspartate transaminase (AST) and/or alanine transaminase (ALT). The values for bilirubin and AST/ALT are usually readily available for cancer patients and are commonly used to evaluate their hepatic function. Therefore by using the results of these tests to characterize the liver impairment in this HV study, its results will be more

relevant to patients with cancer. Finally, it is not clear whether the Child Pugh Classification (CPC) correlates with elimination of drugs metabolized by the liver. CPC lacks the sensitivity to quantitate the capacity of the liver to metabolize individual drugs (Grasela et al., 2000; Khaliq et al., 2000; Shaad et al., 1997, Verbeeck 2008). Although CPC status of subjects will be collected and reported in the two hepatic impairment studies (MEK162; LGX818), enrollment of patients will be performed as a function of their bilirubin and AST/ALT levels rather than by CPC status.

Does the agency agree with this plan?

FDA WRITTEN RESPONSE IN LIEU OF APRIL 29, 2013, MEETING: FDA does not object to Novartis' proposal of enrollment of healthy subjects based on total bilirubin and AST/ALT levels along with collection of CPC status. However, data analysis and determination of potential dosing recommendations should be performed by both CPC status and by total bilirubin and AST/ALT levels. Alternatively, the NCI criteria for hepatic dysfunction based on total bilirubin and AST can be used to enroll cancer patients for these hepatic impairment studies. For LGX818, given its time-dependency, a multiple dose study should be conducted to determine the appropriate LGX818 dose in cancer patients with hepatic impairment.

ADDITIONAL FDA COMMENTS:

6. The statistical analysis plan should be revised to clearly indicate that the primary analyses of PFS will be based only on the pre-specified number of events.

NOVARTIS RESPONSE RECEIVED VIA ELECTRONIC MAIL ON APRIL 26, 2013: Since this is a 3-arm study with a common comparison arm, the timing of the primary analysis must necessarily be synchronized so that sufficient PFS events are obtained for both of the primary comparisons. This may lead to a situation where more than the minimum number of required events will have accrued for one of the comparisons. However, in order to provide as much information as is available, and to comply with the ICHE9 ITT principle, to ensure that all randomized patients contribute to the analysis, it has been proposed to perform the primary PFS analysis when enrollment is complete, each patient is followed for at least one tumor assessment and at least 103 and 302 PFS events for Combination versus vemurafenib and LGX818 versus vemurafenib respectively are available.

Novartis believes the rule described above clearly pre-specifies the timing of primary analysis and therefore proposes to maintain the proposed approach and further discuss with the agency if required.

7. The synopsis states that "Based on a blinded data review, if there are too few patients/events for a given stratum, strata might be grouped or ignored for the analysis. Further details will be provided in the analysis plan. The same principle applies to all

stratified tests and models in this study.” FDA does not accept this proposal, and suggests that Novartis consider using an un-stratified analysis.

NOVARTIS RESPONSE RECEIVED VIA ELECTRONIC MAIL ON APRIL 26, 2013: Several important potential prognostic factors have been included as stratification factors for the randomization. It has been planned to account for these factors in the analysis [ICHE9] by performing a stratified log-rank test. An un-stratified test will also be performed as sensitivity analysis.

Although the randomization strata chosen are expected to lead to relatively even sized strata, the risk for some small strata cannot be excluded. In this case it is proposed to group these with other strata, so as to avoid possible loss of efficiency in log-rank statistics caused by small strata. It is acknowledged that all conventions applied for the statistical analysis should be pre-specified, so the algorithm to be used will be clearly outlined in the statistical analysis plan.

8. FDA recommends that the O’Brien-Fleming method be used to adjust alpha for the OS analyses.

NOVARTIS RESPONSE RECEIVED VIA ELECTRONIC MAIL ON APRIL 26, 2013: Novartis agrees that the O’Brien and Fleming method, which allocates less significance level at an interim analysis, is the most appropriate spending function for a primary endpoint where the study should not be stopped unless the evidence is overwhelmingly convincing.

However, in this study, the first interim analysis for OS is only performed at the time of the primary PFS analysis. The results of the OS interim analysis will therefore not result in early stopping of the study. In this situation it is considered that power considerations can be the guiding principle for the choice of error spending function (Glimm et al, 2010).

The alpha spending function which has been proposed for the OS is based on a Pocock-type boundary implemented using gamma function with parameter 1 ($\alpha=1$), which fully controls the type I error rate at the cumulative alpha level, but more evenly distributes the power. At the time of the primary PFS analysis when the first interim analysis for OS will be performed, approximately 50% of the deaths will have occurred. With the OBF boundary the power for the C vs. V OS comparison would only be 18% vs. 43% using the Pocock-type boundary. It is planned to have 3 OS analyses in the study. Given that the treatment landscape for BRAF melanoma is changing rapidly, OS in this indication is likely to become increasingly confounded, particularly for patients recruited later in the study, it is therefore considered that it is appropriate to allocate reasonable power to the earlier OS interim analyses.

References:

Hierarchical testing of multiple endpoints in group-sequential trials

E. Glimm et al. Stat Med. 2010 Jan 30;29(2):219-28

9. Please specify in the protocol and statistical analysis plan that the final OS analyses will be conducted when 670 deaths have been observed.

NOVARTIS RESPONSE RECEIVED VIA ELECTRONIC MAIL ON APRIL 26, 2013:

Novartis agrees, it will be specified in the protocol and statistical analysis plan that the final OS analysis will be conducted when 670 deaths have been observed.

10. Consider collecting germline DNA from patients enrolled in study CMEK162B2301 to allow for pharmacogenetic analysis in the event outliers are identified. For details, please refer to the Guidance for Industry “*Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling*” at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM337169.pdf>.

NOVARTIS RESPONSE RECEIVED VIA ELECTRONIC MAIL ON APRIL 26, 2013:

Novartis acknowledges FDA’s comment.

3.0 PREA REQUIRMENTS

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 a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

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.

For additional guidance on submission of the PSP, including a PSP Template, please refer to:

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

In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

4.0 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>

5.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion as the sponsor requested the meeting be cancelled and FDA agreed to providing written responses to the pending questions.

5.0 ACTION ITEMS

There are no action items from this meeting.

6.0 ATTACHMENTS AND HANDOUTS

- Addendum consisting of New Information provided by the Sponsor in Sponsor's Response to FDA Draft Preliminary Comments written responses to a new question presented before and during the meeting

ADDENDUM TO FINAL MEETING MINUTES

On April 26, 2013, in a communication sent via electronic mail (e-mail), Novartis submitted new information with their responses to FDA Draft Preliminary Comments that were sent April 25, 2013, for their proposed Phase 3 trial (Protocol CMEK162B2301) entitled, "A Phase 3, Randomized, 3-Arm, Partially Blinded, Placebo Controlled, Multicenter Study of the Combination of LGX818 plus MEK162 Compared with Vemurafenib, and of LGX818 Compared with Vemurafenib for the Treatment of Patients with Unresectable Stage IIIB, IIIC or Stage IV Melanoma with BRAF V600 Mutation.

NOVARTIS COMMUNICATION SENT VIA ELECTRONIC MAIL ON APRIL 26, 2013:

Following submission of the briefing materials to the FDA, additional data from the expansion phase of study CLGX818X2101 (phase I study of LGX818 single agent, IND [REDACTED]^{(b) (4)}) has become available.

By the time the protocol synopsis and briefing book were written, data on 20 patients treated at 450mg/day were available, from 6 patients in the escalation phase (out of 54) and from 14 patients enrolled in the expansion phase. The 6 patients in the escalation phase did not experience any DLT and were treated without any dose interruptions or reductions during the first cycle. Among the 14 patients in the expansion phase, two DLTs were reported: one patient had grade 3 bone pain and vomiting, and one patient had grade 3 myalgia and arthralgia. This data supported the initial recommended dose of 450 mg/day of LGX818 single agent (as included in the protocol synopsis provided with the briefing book).

More data has become available since then. In the expansion phase a total of 32 patients have been enrolled, with median treatment duration of 28 days (1-139 days). Safety data on these patients show that 17 of 32 (53%) patients had grade 3 suspected related AEs, with 16 (50%) occurring during the first cycle, mostly constitutional symptoms (arthralgia, myalgia, fatigue) and nausea/vomiting. Of these 17 patients, 10 patients were dose reduced to 300 mg/d, 2 patients discontinued due to AEs, and 1 patient withdrew consent.

Based on these additional data, the recommended dose for LGX818 single-agent is being revised to 300 mg/d.

The dose of LGX818 in combination with MEK162 is supported by the ongoing Phase Ib/II study CMEK162X2110 (IND 113,850), in which 35 patients have been enrolled (as of 16 April 2013). Based on these data, the recommended dose of LGX818 in combination with MEK162 is 450mg/d (as included in the protocol synopsis). While the MTD in this study has not been reached, two RP2Ds have been declared: 450mg/45mg and 600 mg/45mg for LGX818/MEK162, respectively. One DLT has been reported in the dose escalation phase, a G3 AST/ALT elevation at 600mg/45mg (out of 8 patients treated at this dose level), and no DLT was reported among the 7 patients treated at 450mg/45mg. Notably, based on this preliminary data, on-target toxicities such as hand foot skin reaction, hyperkeratosis, arthralgia, myalgia, and fatigue that are frequently observed with LGX818 single agent, were lessened by the combination with MEK162, resulting in an improved tolerability of LGX818 in the combination. These clinical findings are aligned with the published data suggesting that some of the toxicities of BRAF inhibitors are caused by the paradoxical activation of the MAPK pathway - the addition of a MEK inhibitor (MEK162) to a BRAF inhibitor (LGX818)

likely inhibits this paradoxical activation, making the safety profile of the combination more tolerable.

Therefore, for the purpose of the Phase 3 study CMEK162B2301, the recommended dose of LGX818 will be:

- Single agent: 300 mg/d
- Combination with MEK162: 450 mg/d

As a result, the partial blinding (of the LGX818 arm and the LGX818+MEK162 combination arm) will not be implemented.

Novartis believes that the above mentioned change does not impact the overall design of the study nor the comments provided below by the FDA.

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/s/

ANUJA PATEL
05/28/2013