

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210496Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Review:	June 11, 2018
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 210496
Product Name and Strength:	Braftovi (encorafenib) Capsules, 50 mg and 75 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Array Biopharma Inc.
Submission Date:	May 25, 2018
OSE RCM #:	2017-1306-3
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Division of Oncology Products (DOP2) requested that we review the revised container labels and carton labeling for Braftovi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to a recommendation from the Agency to add the statement “Keep container tightly closed” to the container label and carton labeling^a. The revised container labels and carton labeling also clarify the packaging configurations that Array intends to market as discussed during a teleconference held on May 22, 2018 between members of the review team including DMEPA, DOP2, OPQ; and Array BioPharma Inc. During the call, Array stated that they do not intend to market Braftovi 75 mg capsules in a 60-count bottle^b.

^a Jarrell, K. FDA Communication: Labeling PMR/PMC Discussion Comments Memorandum for Braftovi NDA 210496. Silver Spring (MD): FDA, CDER, OND, OHOP, DOP2 (US); 2018 MAY 23.

^b Jarrell, K. FDA Communication: Internal Meeting Minutes Sponsor T-con for Braftovi NDA 210496. Silver Spring (MD): FDA, CDER, OND, OHOP, DOP2 (US); 2018 MAY 22.

2 CONCLUSION

Our evaluation finds the revised container labels and carton labeling for Braftovi are acceptable from a medication error perspective. We have no further recommendations at this time.

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/s/

JANINE A STEWART
06/11/2018

CHI-MING TU
06/12/2018

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 31, 2018

To: Patricia Keegan, MD
Director
Division of Oncology Products 2 (DOP2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Nazia Fatima, PharmD, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): BRAFTOVI (encorafenib)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 210496

Applicant: Array BioPharma, Inc.

1 INTRODUCTION

On June 30, 2017, Array BioPharma, Inc. submitted for the Agency's review an original New Drug Application (NDA) 210496 for BRAFTOVI (encorafenib) capsules. The proposed indication for BRAFTOVI (encorafenib) capsules is for use in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on August 25, 2017 and August 15, 2017, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for BRAFTOVI (encorafenib) capsules. During the review cycle, DOP-2 determined that BRAFTOVI (encorafenib) tablets requires a Medication Guide (MG) in accordance with 21CFR208. DOP-2 notified the Applicant on February 2, 2018 to convert their proposed PPI into a MG, and to submit it for the Agency's review and approval. The Applicant submitted their proposed MG on February 12, 2018.

2 MATERIAL REVIEWED

- Draft BRAFTOVI (encorafenib) capsules MG received on February 12, 2018, and received by DMPP and OPDP on May 23, 2018.
- Draft BRAFTOVI (encorafenib) capsules Prescribing Information (PI) received on June 30, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 23, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
05/31/2018

NAZIA FATIMA
05/31/2018

LASHAWN M GRIFFITHS
05/31/2018

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: Wednesday, May 30, 2018

To: Anuja Patel, MPH
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

From: Nazia Fatima, PharmD, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP comments on the proposed carton and container labeling for BRAFTOVI™ (encorafenib) capsules for oral use

NDA: 210496

Office of Prescription Drug Promotion (OPDP) has reviewed the proposed carton and container labeling for BRAFTOVI (encorafenib) capsules, for oral use (Braftovi) as requested by Division of Oncology Products (DOP2) in the consult dated August 15, 2017.

OPDP's review of the proposed carton and container labeling is based on the attached proposed carton and container labeling send by electronic mail on May 23, 2018 to OPDP (Nazia Fatima) from DOP2 (Kristen Jarrell). We have reviewed the proposed carton and container labeling and have no comments. OPDP's comments on the proposed draft prescribing information (PI) and patient prescribing information (PPI) were provided under separate covers.

Thank you for your consult. If you have any questions, please contact Nazia Fatima at 240-402-5041 or Nazia.Fatima@fda.hhs.gov.

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/s/

NAZIA FATIMA
05/30/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Review:	May 9, 2018
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 210496
Product Name and Strength:	Braftovi (encorafenib) Capsules, 50 mg and 75 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Array Biopharma Inc.
Submission Date:	April 30, 2018
OSE RCM #:	2017-1306-2
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Division of Oncology Products (DOP2) requested that we review the revised container labels and carton labeling for Braftovi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review memorandum.^a The recommendations were also discussed during a teleconference held on April 25, 2018 between members of the review team including DMEPA, and Array BioPharma Inc.

2 CONCLUSION

Our evaluation finds the revised container labels and carton labeling for Braftovi are acceptable from a medication error perspective. However, we provide a recommendation in Section 3 for a packaging configuration for the Applicant to consider for future development.

^a Stewart, J. Label and Labeling Review Memo for Braftovi (encorafenib) NDA 210496. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 12. RCM No.: 2017-1306-1.

3 RECOMMENDATIONS FOR ARRAY BIOPHARMA INC.

A. General Comments

1. We acknowledge the proposed Braftovi capsules must be dispensed in the original bottle. Because we anticipate that hospital pharmacies may seek to repackage Braftovi capsules for unit-dose dispensing, consider future development to allow the capsules to be dispensed outside of the original bottle or develop unit-dose blister packs for this product in the future.

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/s/

JANINE A STEWART
05/09/2018

CHI-MING TU
05/09/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Review:	April 12, 2018
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 210496
Product Name and Strength:	Braftovi (encorafenib) Capsules, 50 mg and 75 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Array Biopharma Inc.
Submission Date:	February 21, 2018
OSE RCM #:	2017-1306-1
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Division of Oncology Products (DOP2) requested that we review the revised container labels and carton labeling for Braftovi (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

Our evaluation finds the revised container labels and carton labeling for Braftovi may be improved to promote the safe use of this product, and we provide our recommendations in Section 3 and Section 4 below.

^a Stewart, J. Label and Labeling Review for Braftovi (encorafenib) NDA 210496. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JAN 31. RCM No.: 2017-1306.

3 RECOMMENDATIONS FOR THE DIVISION

A. General Comments

1. The Applicant justified the propose Braftovi product should be kept in its original container because the desiccant included in the container is necessary to assure stability through the expiry dating period. However, we anticipate that hospital pharmacies may repackaging Braftovi capsules into unit-dose blister packs. Additional scenarios exist for when a partial quantity may be dispensed by a retail pharmacy, such as when a vacation supply is authorized by insurance or when a cash-paying patient requests a quantity less than a full bottle due to cost considerations. We ask the Review Team to consider asking the Applicant to supply Braftovi in unit-dose blister packs to ensure the safe and effective use of this product. To not hold up treatment options for oncology patients, Braftovi unit-dose blister packs may be introduced after approval of this NDA.

4 RECOMMENDATIONS FOR ARRAY BIOPHARMA INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels and Carton Labeling

1. As currently proposed, the NDC package code (last 2 digits) for container label for 1 bottle (60 or 90 capsules) is **-01 or -02**, and is also **-01 or -02** for the carton labeling of the corresponding strength which contains 2 bottles (120 or 180 capsules). While we acknowledge that your intent is to distribute a carton (2 bottles) as a saleable unit of encorafenib, we anticipate cash paying customers and insurance authorizations of partial quantities (i.e., vacation supply) may lead to dispensing of less than a carton at the pharmacy. Thus, the NDC package code should be different to facilitate verification of the quantity dispensed to prevent wrong quantity dispensing errors. Revise the package codes in the NDC numbers of the container labels and the carton labeling to differentiate the packaging configurations.
2. Revise the statement of quantity to reflect the accurate contents of the carton. For example, carton of "180 capsules" should accurately reflect the contents of the carton as "2 bottles x 90 capsules".

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/s/

JANINE A STEWART
04/12/2018

CHI-MING TU
04/12/2018

**CDRH Consult
MEMORANDUM**

Department of Health and Human Services
Public Health Service
Food and Drug Administration



NDA210496/ICC1600862/S001

DATE: April 2, 2018
RECEIVED: August 28, 2017
TO: Margaret Thompson, M.D./CDER/DOP2
FROM: Caryl Giuliano, Ph.D./CDRH/OIR/DMGP/MGB
THROUGH: Donna Roscoe, Ph.D.
SUBJECT: IND113850

Protocol Title: The COLUMBUS trial (CMEK162B2301) is a 2 Part, Phase 3 Randomized, Open-Label, Phase 3 Multicenter Study of Encorafenib and Binimetinib versus Vemurafenib and Encorafenib Monotherapy in Patients with Unresectable or Metastatic BRAF V600 Mutant Melanoma (Version Number 4, Final: July 13, 2015).

BRAF Codon 600 Mutation Detection by Pyrosequencing—Accuracy Analysis Protocol for COLUMBUS Trial (CMEK162B2301) (Number: PD-0019-DOC-001; September 14, 2017).

Drug Sponsor: Array BioPharma

Drug Name: Encorafenib (BRAFTOVI/LGX818)/ Binimetinib (MEKTOVI/MEK162)

Analyte(s) Detected: BRAF V600E/BRAF V600K mutations

Device: bioMerieux THxID® BRAF Kit (COLUMBUS Trial)/BRAF Codon 600 Mutation Detection by Pyrosequencing (Accuracy Study)

I. BACKGROUND

Array BioPharma has conducted clinical trial CMEK162B2301 (COLUMBUS: Combined LGX818 Used with MEK162 in BRAF mutant Unresectable Skin Cancer), a 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. The objective of this trial was 1) to establish the efficacy of encorafenib plus binimetinib combination therapy in patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation (as detected by an FDA approved test) and 2) to establish the clinical performance of the THxID® BRAF Assay; data collected from this clinical trial has been used to support the supplemental

submission of the THxID® BRAF assay as a companion diagnostic in conjunction with encorafenib plus binimetinib combination therapy.

The THxID® BRAF assay was previously approved as a companion diagnostic for identification of melanoma patients whose tumors carry BRAF V600E and/or BRAF V600K mutations for treatment with (Novartis) trametinib and dabrafenib monotherapies. The THxID®-BRAF kit is a real-time PCR test on the ABI 7500 Fast Dx system (Applied Biosystems Incorporated). The THxID®-BRAF kit is intended for the qualitative detection of the BRAF V600E and V600K mutations in DNA samples extracted from formalin-fixed paraffin-embedded (FFPE) human melanoma tissue.

Supplemental PMA P120014.S008

BioMerieux submitted a 180-day PMA supplement to CDRH [180-day PMA supplement, THxID®- BRAF Kit (PMA120014.S008) Dated June 29, 2017] to support a new intended use for the THxID®- BRAF Assay. PMA120014.S008 was submitted contemporaneous with two NDAs submitted to CDER for approval of encorafenib (NDA210496) and binimetinib (NDA210498), respectively. The THxID®-BRAF Assay was used as a companion diagnostic assay for identifying melanoma patients whose tumors carry BRAF V600E and/or BRAF V600K mutations for treatment with LGX818 (encorafenib) plus MEK162 (binimetinib) combination therapy. The tumor specimens from the screened subjects were tested using the THxID® BRAF assay at four testing laboratories managed by bioMerieux, which functioned as a central laboratory. Testing results were used by clinical sites to determine the subject's enrollment eligibility for the CMEK162B2301 study. Encorafenib is a new-generation BRAF inhibitor for the treatment of melanoma with the V600E mutation in BRAF kinase. Binimetinib is a small molecule MEK inhibitor regulating a key protein kinase in the RAS/RAF/MEK/ERK pathways.

Indications for Use/Rationale for Accuracy Study

The majority of the THxID® BRAF Assay testing was performed according to the instructions for use (IFU) provided in the provisional product package insert for the assay. The IFU of the THxID® BRAF assay specified the sample criteria for DNA extraction as: at least 20mm² of total tissue area with ≥80% tumor content for a 10µm section, or at least 40mm² of total tissue area with ≥80% tumor content for a 5µm tissue section. However, the COLUMBUS trial protocol also allowed the THxID® BRAF testing on specimens that did not meet the IFU specifications, as the Sponsor noted that clinical trial sites had difficulties sourcing specimens within the IFU sample requirements. During screening of the COLUMBUS trial, 152 patients tested positive for BRAF V600E or V600K mutations with specimen(s) not meeting IFU sample requirements. After screening, including all other eligibility requirements for the study, 97 of the 152 patients were enrolled into the COLUMBUS trial with specimen(s) not meeting IFU sample requirements. Via the pre-submission process (Q161899 and Q1618999-S001) and during the face-to-face meeting between CDRH and BioMerieux (June 7, 2017), bioMerieux proposed an accuracy study using DNA extracts from approximately 90 patients, in order to support the use of the THxID® BRAF assay to

detect BRAF V600E and V600K mutant alleles in mutation-positive melanoma FFPE clinical specimens that did not meet IFU sample requirements in the COLUMBUS trial.

P120014.S008 was placed on hold on September 29, 2017 for the following: 1) Major deficiency: pending submission of the accuracy study to CDRH and 2) In order to align the CDRH MDUFA goal date (December 30, 2017) with the CDER PDUFA goal date (June 30, 2018). BioMerieux submitted a draft of the proposed accuracy study for FDA review on November 29, 2017. BioMerieux's formal response to the deficiency is due March 28, 2018 (September 29, 2017 + 180 days). CDRH's decision is due on June 27, 2018 (March 28, 2018 + 90 days). CDER has indicated that they are willing to roll back the PDUFA date from June 30, 2018 to June 27, 2018 to align with the CDRH approval date.

CDER has submitted a consult request for CDRH consult for the THxID® BRAF companion diagnostic assay that will support the testing of subjects in the COLUMBUS Trial. One consult was submitted for encorafenib (NDA210496) and a second consult was submitted for binimetinib (NDA210498). Discussion of the THxID BRAF assay for both NDA is incorporated into this consult report.

Phase 3 Clinical Trial CMEK162B2301

CMEK162B2301 is a 2-Part Phase 3 randomized, open-label, multicenter, parallel group study of LGX818 (encorafenib) plus MEK162 (binimetinib) and LGX818 monotherapy compared with vemurafenib in patients with unresectable or metastatic BRAF V600 mutant melanoma. Testing of patient samples was performed in CLIA-certified laboratories managed by bioMerieux, Inc. There are four central laboratory locations:

(b) (4)
(b) (4) The Primary endpoint of the COLUMBUS trial is PFS of encorafenib plus binimetinib, as compared to vemurafenib.

Part 1:

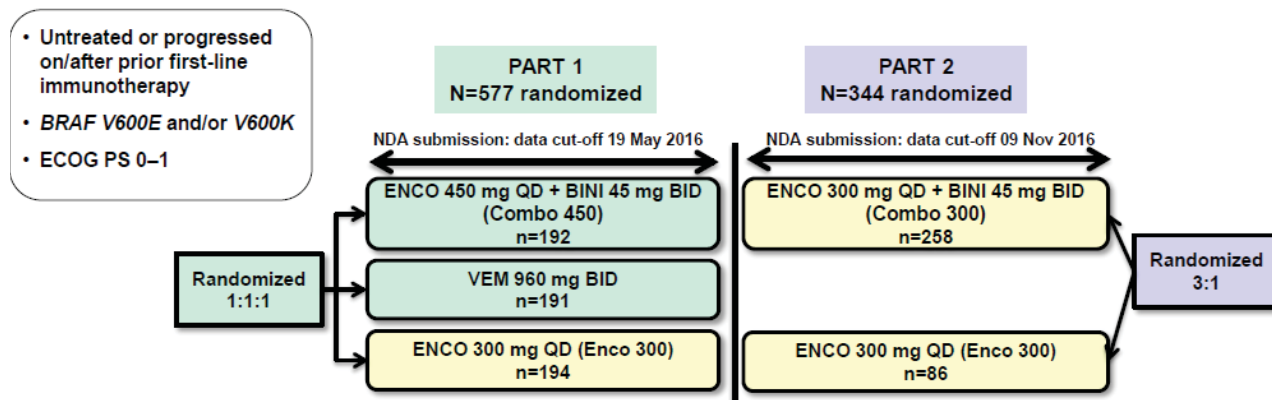
Approximately 576 Patients will be randomized 1:1:1 to one of 3 treatment arms:

- 1) LGX818 450mg QD plus MEK162 45mg BID (Combo 450)
- 2) LGX818 300mg QD monotherapy (LGX818 arm)
- 3) Vemurafenib 960mg BID

Part 2:

Approximately 320 patients will be randomized in a 3:1 ratio to one of 2 treatment arms:

- 1) LGX818 300mg QD plus MEK162 45mg BID (Combo 300)
- 2) LGX818 300mg QD monotherapy (LGX818 arm)



Below is a summary of the total specimens received by all the testing sites and the breakdown of the testing results or final outcomes

Testing Results/Final outcomes	Number Of Specimens				Totals
	Dianon	Genoptix	PMCC	UZA/Esoterix	
NTI	0	81	1	36	118
SRNT	0	65	0	31	96
WT	1	322	11	101	435
INVALID	0	64	1	48	113
QNS	0	36	1	14	51
V600E	1	790	41	432	1264
V600K	0	115	3	50	168
V600E/V600K	0	0	0	2	2
Grand Total	2	1473	58	714	2247

* WT: Wild Type (BRAF V600E & V600K mutation negative); NTI: No Tumor Indicated; QNS: Quantity Not Sufficient to Test; SRNT: Specimen Received, but Not Tested.

Δ A result is defined as "invalid" in the IFU if one of the delta Ct or internal control Ct values falls outside the expected limits.

Distribution of Specimens Received by Tissue Anatomic Locations

Tissue Anatomic Location	Number of Specimens
LYMPH NODE (LN)	512(22.79%, 512/2247)
SKIN (SK)	428(19.05%, 428/2247)
Other*	1307(58.17%, 1307/2247)
Totals	2247

* Since list of code and guideline is not provides to record anatomic location of the tissue, all the tissues not directly labeled as Lymph node or skin were summarized here as "Other".

Summary of characteristics of the specimens tested based on the data from the testing sites pathological evaluation on the H&E slides and PCR testing

	Lymph Node (468)	Skin (394)	Other anatomic locations (1171)	All (2033)†
Tumor Content in the Tissue Section*				
≥80% Tumor content in the tissue section	409(87.39%)	346(87.82%)	1044(89.15%)	1799
<80% Tumor content in the tissue section	59(12.61%)	48(12.18%)	127(10.85%)	234
Total Tissue Area Used for DNA extraction				
Total Tissue area ≥ 20 mm² (10 micro slice) or ≥40 mm² (5 micro slice)	455 (97.22%)	386 (97.97%)	1127 (96.24%)	1968
Total Tissue area < 20 mm² (10 micro slice) or <40 mm² (5 micro slice)	13 (2.78%)	8 (2.03%)	44 (3.76%)	65
Macrodissection performed	337 (72.01%)	341(86.55%)	908 (77.54%)	1586
Melanin Content^Δ	None	285 (60.90%)	189 (47.97%)	705 (60.20%)
	Low	94 (20.09%)	114 (28.93%)	255 (21.78%)
	Medium	36 (7.69%)	54 (13.71%)	113 (9.65%)
	High	53 (11.32%)	37 (9.39%)	98 (8.37%)
Necrosis	182 (38.89%)	99 (25.13%)	379 (32.37%)	660
Fatty Tissue	117 (25.00%)	61 (15.48%)	195 (16.65%)	373
Hemorrhage	167 (35.68%)	99 (25.13%)	373 (31.85%)	639

(*) Tumor Content in the Tissue Section indicates tumor content (%) in the selected tissue area for DNA extraction.

(Δ) Melanin content levels defined per protocol as: Low: ≤10% melanin in the tumor area; Medium: 11% - 24% melanin in the tumor area; High: ≥25% melanin in the tumor area.

(†) The number excludes specimens with no tumor indicated (NTI) and specimens received but not tested (SRNT).

Accuracy Study

An accuracy study was performed to support inclusion of patients whose samples did not meet the IFU requirements in the analysis of the COLUMBUS trial. The objective of this study was to evaluate accuracy, as reflected in the positive percent agreement (PPA) of the THxID® BRAF assay mutation status output to a comparative pyrosequencing method performed by (b) (4) (BRAF Codon 600 Mutation Detection by Pyrosequencing). The specimens for use in this study were specimens provided by Array BioPharma in which the instructions for use IFU sample requirements for the THxID-BRAF® assay were not met.

The IFU of the THxID® BRAF testing defines the sample criteria for DNA extraction as: at least 20 mm² of total tissue area with ≥80% tumor content for a 10µm tissue section, or at least 40 mm² of total tissue area with ≥80% tumor content for a 5 µm tissue section. Due to difficulty in clinical trial sites sourcing specimens within the IFU sample requirements, the protocol was designed to allow the THxID® BRAF testing on specimens that did not meet the IFU specifications.

Table 4a Summary of the THxID™ BRAF results from specimens that meet the IFU requirements and the specimens that did not meet the IFU requirements:

	Specimens did not meet IFU requirements (276)	Specimens met IFU requirements (1757)	Totals
WT	62 (22.46%)	373 (21.23%)	435(21.40%)
Invalid Result	16 (5.80%)	97 (5.52%)	113(5.56%)
QNS	41 (14.86%)	10 (0.57%)	51(2.51%)
V600E	132 (47.83%)	1132 (64.43%)	1264(62.17%)
V600K	25 (9.06%)	143 (8.14%)	168(8.26%)
V600E & V600K	0 (0.00%)	2 (0.11%)	2(0.10%)
Totals	276	1757	2033

COLUMBUS TRIAL Specimens meeting IFU requirements

From the 2033 specimens tested, there were 1757 specimens from 1705 subjects that met the IFU requirements (86.42%, 1757/2033). The testing results from these specimens are as follows:

- 373 specimens are reported as BRAF V600E and V600K mutation negative (WT)
- 1132 specimens are reported as V600E mutation (64.43%)
- 143 specimens are reported as V600K mutation (8.14%)
- 2 specimens are reported as V600E and V600K mutation (0.11%)
- 97 specimens are reported as invalid (5.52%) and 10 specimens are reported as QNS (0.57%)

COLUMBUS TRIAL Specimens not meeting IFU requirements

A total of 276 specimens that did not meet the IFU requirements were tested (13.58%) with the following results reported:

- 62 specimens reported as BRAF V600E and V600K mutation negative (WT) (22.46%)
- 132 specimens reported as V600E mutation (47.83%)
- 25 specimens reported as V600K mutation (9.06%)
- 16 specimens reported as invalid (5.8%)
- 41 specimens reported as QNS (14.86%)

The 276 specimens that did not meet the IFU requirements are associated with 261 subjects. After requesting additional samples for confirmatory testing, there were a total of 319 available specimens for the 261 subjects (including the original specimens and the additional specimens received for confirmatory testing). The final BRAF results after the confirmatory testing and the associated subjects are summarized in Table 4b below:

Table 4b Summary of the THxID™ BRAF results from subjects with samples that did not meet the IFU requirements after confirmatory testing

Final BRAF results after confirmatory testing*	Total Subjects (261)	Total available specimens (319) ^Δ		Subjects with final result reported from specimen meeting the IFU requirements (confirmatory testing)	Subjects with final result reported from specimens not meeting the IFU requirements (original testing and confirmatory testing)
		Specimens not meeting the IFU (original testing and confirmatory testing)	Specimens meeting the IFU (confirmatory testing)		
WT	57	64	15	11	46
Invalid	14	14	7	7	7
QNS	20	23	0	0	20
V600E	143	147	17	14	129
V600K	27	28	4	4	23
Totals	261	276	43	36	225

* Note: In this analysis, the "Final BRAF result" is defined as: 1) if the subject has only one specimen tested, the result from the tested specimen is considered the final BRAF result for the subject; 2) If the subject has multiple specimens tested, and BRAF mutation positive result (V600E, V600K, or V600E/V600K) is available from one or more of the specimens, the BRAF mutation positive result is considered the final BRAF result; 3) If no BRAF mutation positive result (V600E, V600K, or V600E/V600K) is available, then the final BRAF result is determined by: WT>Invalid>QNS and specimen meeting the IFU requirements>specimen not meeting the IFU requirements.

^Δ Total available specimens include the original specimens and specimens for confirmatory testing.

Of the 261 total subjects with samples not meeting the IFU criteria, 152 subjects were either BRAF V600E (129 subjects) or BRAF V600K (23 subjects) mutation positive. After fulfillment of eligibility requirements, 97 subjects were enrolled into the COLUMBUS trial, for which 90 subjects had remnant genomic DNA extracts that were identified for testing by the comparative pyrosequencing method. One sample was lost by the central laboratory and never sent to (b) (4) for testing; therefore, residual genomic DNA extracts from 89 patients tested by the THxID®-BRAF assay and enrolled into the COLUMBUS trial were retrospectively analyzed using the comparative pyrosequencing method (BRAF Codon 600 Mutation Detection by Pyrosequencing) provided (b) (4). (b) (4). The results from the THxID® BRAF assay study were blinded to the (b) (4) staff conducting the accuracy study.

Accuracy Study Samples tested (b) (4)		
Columbus Trial Specimens with final results reported from specimens not meeting the IFU requirements (original testing and confirmatory testing).	V600E positive	129
	V600K positive	23
Total Not meeting IFU and positive V600E/V600K		152
After eligibility requirements for COLUMBUS Number enrolled into Columbus study who did not meet IFU requirements		97
Number of samples with remnant genomic DNA extracts available for use		90
Number lost by central laboratory and never sent (b) (4) for testing		1
Number of samples with residual genomic DNA extracts tested by the THxID™-BRAF assay, enrolled into the COLUMBUS trial and retrospectively analyzed using comparative pyrosequencing method (b) (4)		89

Accuracy Study Results

Pyrosequencing results and the THxID® BRAF assay results of 91 samples (two subjects had duplicate samples) from 89 subjects have been provided.

The PPA and two-sided 95% confidence intervals (CI) were calculated below based on the 89 subjects:

		(b) (4) comparative pyrosequencing method		
		V600*	Suspected V600 ^Δ	Wild-Type
THxID™ BRAF assay	V600*	84	3	2
PPA & 95% CI without suspected V600 subjects		94.38% (84/89) [95%CI 87.38% – 98.15%]		
PPA & 95% CI with suspected V600 subjects		97.75% (87/89) [95%CI 92.12% - 99.73%]		

* In this trial the V600 is defined as V600E, V600K, or V600E/K mutation. ^Δ Suspected V600 in this analysis means that either possible or definitive V600 mutation were detected by pyrosequencing but difficult to definitively call V600E or V600K.

Of the 84 subjects with V600 mutations detected by both pyrosequencing and the THxID™ BRAF assay, 74 subjects had V600E mutations and 10 subjects had V600K mutations detected by both methods. The PPA and 95% CI in the 84 V600 specimens was 94.38% (84/89) [95% CI 87.38% - 98.15%]. Three subjects were called V600 by the THxID™ BRAF assay (2 subjects were called V600E and 1 subject was called V600K), but they could not be called definitively, as such by the pyrosequencing method. Two subjects were reported as V600E mutation by the THxID™ BRAF assay, but called as no mutation detected by pyrosequencing.

II. DEVICE USE IN TRIAL

THxID® BRAF Assay/COLUMBUS Trial

The bioMerieux THxID®-BRAF Assay is intended for the qualitative detection of the BRAF V600E and V600K mutations in DNA samples extracted from FFPE human melanoma tissue. The THxID® is a real-time PCR test on the FDA cleared ABI7500 Fast Dx System. Tumor specimens from the subjects screened in the COLUMBUS Trial (CMEK162B2301) were tested using the THxID® BRAF assay.

The FFPE tissue block was cut into 5µm to 10 µm tissue sections and mounted on glass slides (if unstained slides were received, the slides were used directly for the following steps); hematoxylin and eosin (H&E) staining was performed on one slide. The H&E slide was pathologically evaluated using specifications defined in the IFU; tumor tissue from the unstained slides was scraped for DNA extraction based on the pathological evaluation; total DNA was extracted from the scraped tumor tissue using silica technology; the extracted DNA was analyzed using the THxID® BRAF kit on the FDA cleared ABI 7500 Fast Dx PCR instrument. The SDS files from the ABI 7500 Fast Dx PCR instrument were analyzed using THxID® BRAF software to generate the testing result.

BRAF Codon 600 Mutation Detection by Pyrosequencing/Accuracy Analysis

The purpose was to evaluate the accuracy, as reflected in the positive percent agreement (PPA) of the THxID® BRAF Assay mutation status output to a pyrosequencing [on the

PyroMark Q24 instrument (Qiagen)] comparative method offered by (b) (4) in specimens in which the IFU sample requirements were not met.

Residual genomic DNA extracts from 90 patients that were tested by the THxID® BRAF assay and enrolled into the COLUMBUS trial were retrospectively analyzed using the comparative pyrosequencing method provided (b) (4). Genomic DNA eluates were stored at -70° C (b) (4). These eluates were shipped on dry ice from (b) (4) prior to execution of the study protocol. Eluates remained in storage at -30° C or colder upon receipt at (b) (4). Eluates were thawed for use with the comparative pyrosequencing method and returned to the -30° C or colder storage after sample analysis was completed. All samples were run with a no template control, a positive control and a negative V600 wildtype control. Acceptable peak height for patient samples was above 20 RFU. Sample replicate well allele frequency needed to be within 4% of each other in order for sample results to be accepted. The specimen will be repeated if allele frequency results indicate a large discordance between replicates (e.g., 10% and 25% allele frequency outputs). Specimen result output was reported as **Not Detected** (a mutation in BRAF codon 600 was not detected) or **Positive** (A mutation in BRAF codon 600 was detected).

III. CDRH Comment to CDER:

The Accuracy study provided to CDRH, in support of the use of patient samples not meeting IFU sample requirements in the COLUMBUS trial, is acceptable.

CDRH has no further comments or issues in regard to use of the THxID® BRAF Assay in the COLUMBUS Trial or for the new intended use. CDRH is working with bioMerieux on the labeling for the THxID® BRAF Assay for the new intended use.

As noted, CDRH requests that the CDER PDUFA goal date of June 30, 2018 be changed to June 27, 2018, in order to align with the CDRH MDUFA goal date. CDER has indicated that the change to June 27, 2018 is acceptable.

Reviewer Note: The formal submission for P120014/S008 was submitted to CDRH on March 16 (inadvertently, as it was supposed to be submitted on March 28, 2018 for a June 27th approval).

Receipt of the formal supplement brings it off the 'hold' status and re-starts the 90 day clock (March 16th + 90 days= MDUFA date of June 16th Saturday, so really June 15th—Friday).

Since CDRH already requested the June 27th date from CDER and CDER agreed, we will send a non-approvable letter to bioMerieux-then bioMerieux can respond to CDRH and request to have the device approved contemporaneous with drug approval on June 27, 2018.



Caryl Giuliano -S
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/s/

CARYL J GIULIANO
04/02/2018

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****PRE-DECISIONAL AGENCY MEMO****

Date: March 23, 2018

To: Anuja Patel, MPH
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

From: Nick Senior, PharmD, JD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Comments on the proposed product labeling for NDA 210496
BRAFTOVI (encorafenib) capsules, for oral use

OPDP has reviewed the proposed product labeling (PI) for BRAFTOVI (encorafenib) capsules, for oral use (Braftovi) as requested in the consult dated August 15, 2017. The following comment, using the proposed substantially complete, marked-up version of the PI emailed to OPDP by Anuja Patel on March 10, 2018, is provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed and comments on the proposed patient labeling will be sent under separate cover.

12.1 Mechanism of Action – OPDP recommends revising the statement, “Encorafenib is a kinase inhibitor that targets BRAF V600E, as well as wild-type...” (emphasis added) due to the potential promotional usage of this terminology. We note that “target” is used in the discussion of Braftovi with Mektovi later in this section of the PI; however, this language is consistent with the product’s competitors.

Thank you for your consult. If you have any questions, please feel free to contact Nicholas Senior at 240-402-4256 or Nicholas.Senior@fda.hhs.gov

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/s/

NICHOLAS J SENIOR
03/25/2018



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: January 18, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Anuja Patel, RPM
DOP2

Subject: QT-IRT Consult to NDA 210496

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This memo acts as an addendum to our earlier review for NDA 210496 dated 12/14/2017 in DARRTS and provides labeling language for Section 5, and changes to labeling language for Section 12 of the label. The QT-IRT reviewed the following materials:

- [Sponsor's proposed labeling language](#);
- [Previous QT-IRT review](#) dated 12/14/2017 in DARRTS; and
- [Approved product label for KISQALI® \(ribociclib\)](#).

The following is QT-IRT's proposed labeling language, which is a suggestion only. The provided language is modeled based on approved product label for KISQALI® (ribociclib). We defer the final labeling decisions to the Division.

5.x QT Prolongation

BRAFTOVI has been shown to prolong the QT interval in a dose-dependent manner, with estimated mean increase in QTc interval of 18 ms (90% CI: 14, 22)) after administration of recommended therapeutic dose of BRAFTOVI in combination with binimetinib to adult patients with cancer [see *Clinical Pharmacology* (12.2)]. In addition, following administration of recommended therapeutic dose of BRAFTOVI in combination with binimetinib, 5%

(13/268) of patients experienced Δ QTcF greater than 60 ms and 1% (2/268) of patients had the incidence of new QTcF greater than 500 ms. There were no reported cases of Torsades de Pointes.

Avoid the use of BRAFTOVI in patients who already have or who are at significant risk of developing QTc prolongation, including patients with congenital long QT syndrome, uncontrolled or significant cardiac disease or conduction abnormalities such as congestive heart failure, bradyarrhythmias, and electrolyte abnormalities.

Avoid the use of BRAFTOVI with drugs known to prolong the QTc interval, and/or strong CYP3A inhibitors as this may lead to prolongation of the QTc interval [see *Clinical Pharmacology* (12.3)].

Based on the observed QT prolongation during treatment, BRAFTOVI may require dose interruption, reduction or discontinuation as described in Table 2 [see *Dosage and Administration* (2.3)].

12.2 Pharmacodynamics

Cardiac Electrophysiology

Encorafenib is associated with dose-dependent QTc interval prolongation. Following administration of recommended therapeutic dose of encorafenib in combination with binimetinib to adult patients with cancer, the mean (90% CI) QTcF change from baseline (Δ QTcF) was 18 (14-22) ms [see *Warnings and Precautions* (5.x)].

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

DHANANJAY D MARATHE
01/18/2018

CHRISTINE E GARNETT
01/18/2018

Clinical Inspection Summary

Date	12/28/2017
From	Navid Homayouni, M.D., Medical Officer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Anuja Patel, Regulatory Project Manager Margaret Thompson, M.D., Clinical Reviewer Ashley Ward, M.D., Cross Discipline Team Leader Division of Oncology Products 2
NDA #	210496 and 210498
Applicant	Array BioPharma Inc.
Drug	BRAFTOVI (encorafenib) for NDA 210496 and MEKTOVI (binimetinib) for NDA 210498
NME (Yes/No)	No
Therapeutic Classification	Priority
Proposed Indication(s)	Encorafenib in combination with binimetinib for treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test
Consultation Request Date	July 19, 2017
Summary Goal Date	February 1, 2018
Action Goal Date	June 29, 2018
PDUFA Date	June 29, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study CMEK162B2301 was submitted to FDA in support of a proposed indication for NDA 210496 (encorafenib) and NDA 210498 (binimetinib) for both products to be administered together as a combination. This was a 2-part phase III randomized, open label, multicenter study. The focus of this inspection is Part 1 of this study and clinical investigator site selection was accordingly based on Part 1 of the study. Four clinical sites, Dr. Ivana Krajsova, M.D. (Site 3012), Dr. Caroline Dutriaux, M.D. (Site 3046), Dr. Ralf Gutzmer, M.D. (Site 4015), Dr. Thaddeus Beck, M.D. (Site 5048), and the Contract Research Organization (CRO), (b) (4) were selected for audit.

The data for Study CMEK162B2301 submitted by the Sponsor to the Agency in support of NDA 210496 and NDA 210498 appear reliable based on available information from the inspections of four clinical sites and the CRO. There were no significant inspectional observations for clinical investigators Dr. Ivana Krajsova, M.D., Dr. Caroline Dutriaux, M.D.,

Dr. Ralf Gutzmer, M.D., and the CRO, (b) (4). The preliminary classification for the inspections of Drs. Krajsova, Dutriaux, and Gutzmer and the preliminary classification for the inspection of (b) (4) is No Action Indicated (NAI).

Although regulatory violations were observed during the inspection of Dr. Thaddeus Beck M.D., these violations are unlikely to significantly impact the determination of efficacy and safety and the preliminary classification for the inspection is Voluntary Action Indicated (VAI). However, it is recommended that a sensitivity analysis with and without the data from Site 5048 be performed.

A Clinical Inspections Summary Addendum will be provided if the final classifications of the inspections of the clinical investigators and CRO are significantly different following receipt and review of the Establishment Inspection Report (EIR).

II. BACKGROUND

Array BioPharma Inc. is seeking approval to market encorafenib (LGX818) and binimetinib (MEK162) in combination for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test. Study CMEK162B2301 entitled “A 2-part phase III randomized, open label, multicenter study of LGX818 plus MEK162 versus vemurafenib and LGX818 monotherapy in patients with unresectable or metastatic *BRAF* V600 mutant melanoma” forms the basis for the clinical evaluation of encorafenib and binimetinib for the determination of safety and efficacy.

Study CMEK162B230, Part 1, was a three-arm study, comparing the efficacy and safety of encorafenib plus binimetinib to vemurafenib and encorafenib monotherapy in patients with locally advanced unresectable or metastatic melanoma with *BRAF* V600 mutation. The primary efficacy endpoint was progression-free survival (PFS) of Combo 450 (MEK162 at 45 mg and LGX818 at 450mg) vs vemurafenib monotherapy. PFS was defined as the time from the date of randomization to the date of the first documented progression or death due to any cause, whichever occurred first.

The study was conducted from November 20, 2013 to May 19, 2016. There were 577 subjects randomized to treatment in Part 1 (192 Combo 450 arm, 194 encorafenib arm and 191 vemurafenib arm). Subjects were randomized at 162 clinical sites in 28 countries which consisted of 20 sites in North America, 124 sites in Europe and 18 sites in selected countries from the rest of the world.

As reported by the Sponsor, the primary objective of the study was met as Study CMEK162B230, Part 1, demonstrated significantly improved PFS for Combo 450 vs vemurafenib alone by more than doubling the PFS.

GCP inspection was conducted at a CRO site and at four clinical investigator (CI) sites. The CI sites for inspection were chosen because of high enrollment and study results by site.

III. RESULTS (by site):

Name of CI, Site #, Address, Country if non- U.S. or City, State if U.S.	Protocol # # of Subjects	Inspection Dates	Classification
Ivana Krajsova, M.D. Site Number: 3012 U Nemocnice 2 Praha, 128 08 Czechoslovakia	Protocol: Part 1 CMEK162B2301 Number of Subjects Enrolled: 8	October 30- November 2, 2017	Pending: Preliminary NAI
Caroline Dutriaux, M.D. Site Number: 3046 1 Rue Jean Burguet Bordeaux, Gironde 33075 France	Protocol: Part 1 CMEK162B2301 Number of Subjects Enrolled: 14	October 16-20, 2017	Pending: Preliminary NAI
Ralf Gutzmer, M.D. Site Number: 4015 Carl-Neuberg-Strasse 1 Hannover, 30625 Germany	Protocol: Part 1 CMEK162B2301 Number of Subjects Enrolled: 9	October 23-27, 2017	Pending: Preliminary NAI
Thaddeus Beck, M.D. Site Number: 5048 3232 North Northhills Boulevard Fayetteville, AR 72703	Protocol: Part 1 CMEK162B2301 Number of Subjects Enrolled: 7	November 13-16, 2017	Pending: Preliminary VAI
CRO: (b) (4) (b) (4)	Protocol: Part 1 CMEK162B2301	(b) (4)	Pending: Preliminary NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Ivana Krajsova, M.D. (Site 3012)

The clinical site screened 21 subjects and 8 were enrolled and randomized. At the time of the inspection, 2 subjects were still on study treatment; all others had completed the study and were either discontinued due to disease progression or adverse events. An audit of all subject's records was conducted.

The inspection evaluated all subject informed consent forms, subject eligibility, test article accountability, blinding/randomization procedures, source documents, primary endpoint, and adverse events to determine overall protocol compliance. Study source documents and records of the audited subjects were compared to the data listings and found to be the same.

There were no objectionable conditions noted, and no Form FDA-483, Inspectional Observations was issued. The primary efficacy endpoint data, PFS as determined by the site investigator, were verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 3012 appear reliable based on available information.

2. Caroline Dutriaux, M.D. (Site 3046)

The site screened 21 subjects and 14 subjects were enrolled and randomized. At the time of the inspection, one subject was still ongoing in the trial; all others had completed the study and were either discontinued due to disease progression or adverse events. An audit of all subject's records was conducted.

The inspection evaluated all subject informed consent forms, subject eligibility, test article accountability, blinding/randomization procedures, source documents, primary endpoint, and adverse events to determine overall protocol compliance. Study source documents and records of the audited subjects were compared to the data listings and found to be the same.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued. The primary efficacy endpoint data, PFS as determined by the site investigator, were verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 3046 appear reliable based on available information.

3. Ralf Gutzmer, M.D. (Site 4015)

The site screened 20 subjects and 9 were enrolled and randomized. At the time of the inspection, two subjects were still on study treatment; all others had completed the study and were either discontinued due to disease progression or adverse events. An audit of all screened and enrolled subject's records was conducted.

The inspection evaluated all subject informed consent forms, subject eligibility, test article accountability, blinding/randomization procedures, source documents, primary endpoint, and adverse events to determine overall protocol compliance. Study source documents and records

of the audited subjects were compared to the data listings and found to be the same.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued. The primary efficacy endpoint data, PFS as determined by the site investigator, were verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 4015 appear reliable based on available information.

4. Thaddeus Beck, M.D. (Site 5048)

The site screened 19 subjects and 8 subjects were enrolled and randomized. At the time of the inspection, one subject was still on study treatment; all others had completed the study and were either discontinued due to disease progression or adverse events. An audit of all screened and enrolled subject's records was conducted.

The inspection evaluated subject informed consent forms, screening and enrollment logs, source records, subject diaries, drug accountability logs, sponsor monitoring files and correspondence. Study source documents and records of the audited subjects were compared to the data listings and found to be the same.

Review of all regulatory documentations showed no irregularities. However, a Form FDA-483 was issued for "Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation". Specifically, case histories including the case report forms and supporting data for protocol CMEK162B2301 were not properly retained for 8 of 8 subjects enrolled at the site with the following observations:

1. The paper source records maintained in the case history files for all enrolled subjects were shredded after the records were scanned and imported into ARIA and OncoEMR electronic medical record systems. These records include but are not limited to case report forms, doctor notes, laboratory requisition forms and laboratory results.
2. Per site's SOP Number: 7 titled Data Management, "The PI and/or CRC should obtain written notification from the sponsor prior to any record destruction." There is no written documentation of approval from the sponsor to shred subject case history source records. Additionally, there is no documentation within regulatory records which communicates subject case history records were shredded after scanning them into electronic medical records system.
3. The primary investigator (PI) did not have any written assurance or certification for the accuracy and completeness of the 8 subject case histories that were scanned into your EMR system and then shredded.

OSI Reviewer Comment:

For all subject source records shredded after being scanned into the electronic medical record systems prior to May 2016, the staff at the site placed a stamp on the scanned records

indicating “Scanned”. This was the old practice which affected the records reviewed during the inspection. The site does have a new process in line to document the accuracy of scanning the records by accompanying the scans with an electronic signature and a statement verifying the accuracy of the scanned records. However, the new system does not affect the records reviewed during the inspection. Furthermore, the site was unable to provide a certification letter from a third party that scanned over the documents.

*Given that the site shredded original subjects source records and was unable to produce documentation verifying that the copy of the original records has all the same attributes and information as the original records through certification, **OSI recommends that a sensitivity analysis with and without the data from Site 5048 be performed.***

Although regulatory violations were noted at the clinical site, they do not appear to significantly impact study outcomes, or have placed subjects at undue risk. Overall, the PI had good oversight of the study. The primary efficacy endpoint data, PFS as determined by the site investigator, were verifiable by comparing eCRF and data listings with the scanned records. There was no evidence of under reporting of AEs.

5. CRO [REDACTED] (b) (4)

The inspection was issued to review the conduct of clinical study (CMEK162B2301, Part 1), performed in support of the application. The inspection focused on financial disclosures, temperature log, training log, electronic case report forms, data collection and security policies, and standard operation procedures/ policies. Assessment of [REDACTED] (b) (4) conduct of CRO responsibilities included overall project management, data management, site monitoring, statistical programming and Trial Master File (TMF) management.

The inspection found no major regulatory violations or deficiencies. There was appropriate oversight and management of Study CMEK162B2301, Part 1. A form FDA 483, Inspectional Observation was not issued. The data from [REDACTED] (b) (4), associated with Study CMEK162B2301, Part 1, appear reliable based on available information.

{See appended electronic signature page}

Navid Homayouni, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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cc:

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OSI/DCCE/GCP Reviewer/Navid Homayouni

OSI/ GCP Program Analysts/Yolanda Patague/Joseph Peacock

OSI/Database PM/Dana Walters

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/s/

NAVID N HOMAYOUNI
12/28/2017

SUSAN D THOMPSON
12/28/2017

Interdisciplinary Review Team for QT Studies Consultation: QT Study Review

NDA	210496
Brand Name	Encorafenib
Generic Name	BRAFTOVI
Sponsor	Array BioPharma, Inc.
Indication	In combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test
Dosage Form	Capsules: 50 mg and 75 mg
Drug Class	Protein kinase inhibitor
Therapeutic Dosing Regimen	450 mg orally QD in combination with binimetinib 45 mg BID
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	450 mg QD when in combination with 45 mg BID binimetinib
Submission Number and Date	001; 6/30/2017
Review Division	DOP2

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1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

Encorafenib is associated with dose-dependent QTc interval prolongation. This conclusion is based on data from studies CLGX818X2109 and CLGX818X2101, which also showed an upper bound of the 2-sided 90% confidence interval >20 ms for mean change in QTcF from baseline for encorafenib 450 mg QD monotherapy and encorafenib 450 mg QD in combination with 45 mg BID binimetinib (Table 1). The studies did not include placebo or positive controls. The QTc effects for binimetinib were evaluated in a prior QT-IRT review (NDA (b) (4), review dated 12/20/2016 in DARRTS), and it was concluded that no large mean QTc prolongation (20 ms) is estimated following 45 mg BID dosing of binimetinib.

Study CLGX818X2109 was 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. In this study, 75 patients were in BRAF/MEK-treatment naïve group, and were administered with Combo 450 (450 mg QD encorafenib + 45 mg BID binimetinib) dosing regimen.

Study CLGX818X2101 was a Phase 1, open-label, multicenter study of encorafenib monotherapy in adult patients with cancer. The study was comprised of a dose-escalation phase and a dose-expansion phase. In the dose expansion phase of the study 17 patients and 34 patients were administered with 300 mg QD and 450 mg QD encorafenib dosing regimen, respectively.

Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for encorafenib as a single agent (300 mg QD and 450 mg QD) and 450 mg QD of encorafenib in combination with 45 mg BID binimetinib (Combo 450) (CLGX818X2101 and CLGX818X2109, FDA Analysis)

Study	Treatment	N	Time (hour)	Δ QTcF Mean (ms)	Δ QTcF Std Dev	Δ QTcF 90% CI (ms)
CLGX818X2101	300 mg QD encorafenib	13	Day 15, 2 h post-dose	12.9	11.1	(6.9, 18.9)
	450 mg QD encorafenib	19	Day 15, 2 h post-dose	19.9	16.6	(13.3, 26.5)
CLGX818X2109	450 mg QD encorafenib in combination with 45 mg BID binimetinib	66	Week 6, Day 1, 1.5 h post-dose	18.3	18.7	(14.4, 22.1)

The therapeutic dose of encorafenib 450 mg QD in combination with binimetinib 45 mg BID is deemed as the maximum tolerated dose (MTD). Encorafenib is primarily metabolized and eliminated by liver, and patients with moderate/severe hepatic impairment may have increased exposure. Encorafenib is metabolized by CYP3A4, CYP2C19 and CYP2D6, with CYP3A4 predicted to be the major contributor to clearance. In DDI study in healthy subjects, co-administration of strong (posaconazole) and moderate (diltiazem) CYP3A4 inhibitors with encorafenib resulted in an increase in $C_{\max}$ (1.7- and 1.4-fold higher) and AUC (3- and 2-fold higher) for encorafenib. QTc prolongation at these higher exposure scenarios are not covered by the QTc data in studies CLGX818X2101 and CLGX818X2109.

Even though encorafenib show a dose- and concentration-dependent QTc interval prolongation, there is a lack of direct relationship between concentrations of encorafenib and QTc effects because of temporal increase in QTc effects ($C_{\max}$ after multiple dosing is lower than the $C_{\max}$ after the first dose on Day 1, but post-dose Δ QTc after multiple dosing is higher compared to post-dose Δ QTc on Day 1). Therefore, a linear C-QTc model that assumes a direct relationship between plasma concentrations and QTc cannot be used for analysis.

2 PROPOSED LABEL

This section contains the sponsor's proposed labeling related to the QTc effects, QT-IRT's proposed labeling and comments to the sponsor regarding the labeling changes.

Sponsor's proposed labeling

2.3 Dose Modifications

Table 1: Recommended Dose Reductions for BRAFTOVI

First Dose Reduction	300 mg orally once daily
Second Dose Reduction	200 mg orally once daily
Subsequent Modification	Permanently discontinue (b) (4) if unable to tolerate 200 mg (b) (4) once daily

Table 2: Recommended Dose Reductions for BRAFTOVI*QTc Prolongation*

(b) (4)

12.2 Pharmacodynamics

Cardiac Electrophysiology

A (b) (4) QT study to evaluate the QT prolongation potential of encorafenib has not been conducted. Encorafenib is associated with (b) (4)-dependent QT interval prolongation.

(b) (4)

QT-IRT's proposed labeling

The dose modifications proposed by the sponsor in Section 2.3 of the label, as stated above, are acceptable. However, for Section 12.2, QT-IRT's proposed labeling language is as follows, which is a suggestion only and we defer the final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Encorafenib is associated with dose-dependent QTc interval prolongation. Following administration of recommended therapeutic dose of encorafenib in combination with

If the changes in Section 12.2 labeling are acceptable to the Division, the following comments could be used while communicating the labeling edits to the sponsor.

Comments for the sponsor:

(b) (4)

3 BACKGROUND

3.1 PRODUCT INFORMATION

Encorafenib is a novel oral small-molecule kinase inhibitor with potent and selective inhibitory activity against mutant BRAF kinase, a member of the RAF/MEK/ERK MAPK pathway, which plays a prominent role in controlling several key cellular functions including growth, proliferation, and survival.

3.2 MARKET APPROVAL STATUS

Encorafenib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

Preclinical evidence to date suggests that encorafenib lacks appreciable inhibition of human ether-a-go-go-related gene mediated signaling (hERG; IC₅₀ = 73.4 μM) (Study # Pcs-r 0970564 (b) (4) Study No. 090926.OPW). In a study conducted under Good Laboratory Practice (GLP), 4- and 13-week oral (gavage) toxicity studies in monkeys and a GLP monkey telemetry study, encorafenib had no effect on ECG morphology, heart rhythm or PR interval (PR), QRS interval (QRS), QT and QTc interval (Study #Pcs-r1170383 (b) (4) Study no. 694467). Additional analysis of a major phase I metabolite of encorafenib, AR00492720 (also referred to as LHY746), also has a minimal effect on hERG (IC₅₀ = 69.0 μM) ((b) (4) Study # 100033086-0).

3.4 CLINICAL PHARMACOLOGY

Appendix 7.1 summarizes the key features of encorafenib's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the general assessment and analysis proposal for ECG assessments in sponsor's planned clinical studies prior to conducting the studies under IND 113850. The QT-

IRT considered QT assessment for the combination therapy of encorafenib and binimetinib acceptable. However, QT-IRT also recommended that the sponsor implement the original QT assessment plan for binimetinib and encorafenib alone. Sponsor submitted the study report CP-17-005 and CP-17-006 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 QT STUDIES

4.2.1 Title

CP-17-005: Cardiac Safety and Concentration-QT Interval Analysis of Single Agent Encorafenib Data from Clinical Study CLGX818X2101

CP-17-006: Cardiac Safety and Concentration-QT Interval Analysis of Combination Encorafenib and Binimetinib Data from Clinical Studies CMEK162X2110, CLGX818X2109 and CMEK162B2301

4.2.2 Protocol Number

CP-17-005 (Study CLGX818X2101)

CP-17-006 (Pooled data from Studies CMEK162X2110, CLGX818X2109 and CMEK162B2301)

4.2.3 Study Dates

Data cut-off date for interim report:

CLGX818X2101: 08-18-2014

CMEK162X2110: 08-31-2015

CLGX818X2109: 02-18-2016

CMEK162B2301: 11-09-2016

4.2.4 Objectives

CP-17-005 (Study CLGX818X2101):

The primary objective of the cardiac safety and C-QT analysis was to evaluate the potential of therapeutic concentrations of encorafenib to delay cardiac repolarization as measured by QT prolongation. The analysis was completed using encorafenib concentrations and ECG measurements from clinical study CLGX818X2101, a dose escalation and expansion study in patients with metastatic melanoma and metastatic colorectal (mCRC) conducted with expanded ECG monitoring. The following analyses were performed to support the above objective:

- Characterize the relationship between encorafenib concentration and Δ QT interval using time-matched concentration and QT data and a LME model.
- Characterize measures of central tendency for appropriate ECG (QT and HR) measurements across nominal timepoints at Tmax and as a maximum across patients.
- Tabulate incidences of morphological ECG tracing abnormality shifts from Baseline.

CP-17-006 (Pooled data from Studies CMEK162X2110, CLGX818X2109 and CMEK162B2301):

The primary objective of this analysis was to evaluate the potential therapeutic concentrations of encorafenib and binimetinib that could delay cardiac repolarization as measured by QT prolongation. The analysis was completed using encorafenib concentrations and ECG measurements from clinical studies CMEK162X2110, CLGX818X2109 and CMEK162B2301.

The following analyses were performed to support the above objective:

- Characterize the relationship between encorafenib and binimetinib concentrations and Δ QT interval using time-matched concentration and QT data and a LME model.
- Characterize measures of central tendency for appropriate ECG (QT) measurements across nominal timepoints, including at T_{max} (approximately 1.5 hours postdose), and as a maximum across patients.

4.2.5 Study Description

4.2.5.1 Design

See Section 4.2.8.1.

4.2.5.2 Controls

No placebo or positive control for ECG.

4.2.5.3 Blinding

All studies were open-label studies.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

See Section 4.2.8.1. The treatment arms of interest for this review were as follows:

CLGX818X2101: 300 mg QD and 450 mg QD of encorafenib monotherapy.

CLGX818X2109: Combo 450 (450 mg QD encorafenib in combination with binimetinib 45 mg BID)

CMEK162X2110: Combo 450

CMEK162B2301: Combo 450

4.2.6.2 Sponsor's Justification for Doses

Combo 450 is MTD dosing regimen.

Reviewer's Comment: Encorafenib 450 mg in combination with binimetinib 45 mg is the MTD for combination therapy. Age, gender or body weight have no clinically meaningful effect on the systemic exposure of encorafenib. A dedicated clinical trial indicates a 25% higher encorafenib exposure in patients with mild hepatic impairment (Child-Pugh Class A) compared with subjects with normal liver function. As encorafenib is primarily metabolized and eliminated via the liver, patients with moderate to severe hepatic impairment may have increased exposure. In healthy subjects, co-administration of strong (posaconazole) and moderate (diltiazem) CYP3A4 inhibitors with encorafenib resulted in an increase in overall (AUC, 3- and 2-fold higher, respectively) and peak (C_{max}, 68.3% and 44.6% higher, respectively) encorafenib exposure. There was no accumulation of exposure with multiple dosing of encorafenib. C_{max} on Day 15 was observed to be less than that on Day 1 in both monotherapy (300 mg QD and 450 mg QD) and combination regimen (450 mg QD) with binimetinib.

4.2.6.3 Instructions with Regard to Meals

Encorafenib can be administered with or without food.

Reviewer's Comment: There was a lack of a food effect on the extent of exposure to encorafenib following a single oral 100 mg dose (Study ARRAY-818-102).

4.2.6.4 ECG and PK Assessments

CP-17-005 (Study CLGX818X2101):

ECG: A standard 12-lead ECG was performed in triplicate at screening. After screening, duplicate ECGs were conducted at the following predose times:

- During cycle 1 on day 1, 2, 8, 15, 16 and 22
- Day 1 of all subsequent cycles
- End of treatment (EOT)

On Day 1 and Day 15 of Cycle 1, 0.5 hours, 2 hours, 6 hours and 24 hours (predose on Day 2 and Day 16, respectively), postdose ECGs were also conducted. These postdose ECGs were performed for patients enrolled in the dose-escalation phase and only at times when the pharmacokinetic (PK) samples were collected during the expansion phase. On all occasions, the ECG was performed immediately before the corresponding PK sample time. For patients enrolled in the expansion phase with no PK samples collected, only the 2 hour postdose ECGs were performed in addition to the predose ECGs on Day 1 and Day 15 of Cycle 1.

ECGs were electronically transmitted and independently reviewed by a central reading facility.

PK: Samples for PK analysis were collected on Cycle 1 Day 1 and Cycle 1 Day 15 at predose, 0.5, 2, 4, 6, 8, 10 (BID regimen only) and 24 hours postdose. On Cycle 1 Day 8, samples were collected at predose, 0.5, 2, 4, 6, 8 hours postdose. Predose samples were collected from Cycle 2 Day 1 to Cycle 10 Day 1 as well as at the EOT visit. PK samples were to be collected only for the first 10 patients enrolled in each patient group (A, B and C) and if required for more patients in the expansion phase and all patients enrolled in the dose escalation.

CP-17-006 (Pooled data from Studies CMEK162X2110, CLGX818X2109 and CMEK162B2301):

The PK and ECG collection times for the source studies are summarized in Table 2

Table 2.

Table 2: PK/ECG assessments from Encorafenib and Binimetinib combination studies

Binimetinib / Encorafenib dual combo study	Nominal ECG Collection Time	Nominal PK Collection Time
CLGX818X2109 (LOGIC2)	Triplicate ECG: Cycle 1 Day 1 pre-dose (Baseline ECG) Single ECG: Cycle 1 Day 1 1.5 hours post-dose Cycle 1 Day 15 pre-dose Cycle 1 Day 15 1.5 hours post-dose Cycle 2 Day 8 pre-dose and 1.5 hours post-dose Cycle 2 Day 21 pre-dose and 1.5 hours post-dose Cycle 3 Day 15 pre-dose and 1.5 hours post-dose Every other subsequent cycle Day 15 pre-dose and 1.5 hours post-dose End of Treatment	Cycle 1 Day 1 1.5 hours post-dose Cycle 1 Day 15 pre-dose Cycle 1 Day 15 1.5 hours post-dose Cycle 2 Day 8 pre-dose Cycle 2 Day 21 pre-dose Cycle 3-5 Day 15 pre-dose End of Treatment Unscheduled
CMEK162X2110	Triplicate ECG: Cycle 1 Day 1 pre-dose Single ECG: Cycle 1 Day 15 pre-dose Cycle 2 Day 1 pre-dose Cycle 2 Day 15 pre-dose Day 1 of subsequent cycles pre-dose End of Treatment	Phase I: Cycle 1 Day 1 pre-dose and 0.5, 1.5, 2.5, 4, 6, 8, 24 hours post-dose Cycle 1 Day 15 pre-dose and 0.5, 1.5, 2.5, 4, 6, 8, 24 hours post-dose Cycle 2-10 Day 1 pre-dose Unscheduled Phase II: Cycle 1 Day 1 pre-dose and 0.5, 1.5,

		2.5, 5, 8, 24 hours post-dose Cycle 1 Day 15 pre-dose and 0.5, 1.5, 2.5, 5, 8, 24 hours post-dose Cycle 2-10 Day 1 pre-dose Unscheduled
CMEK162B2301 (COLUMBUS)	Triplicate ECG: Screening Single ECG: Cycle 1 Day 1 1.5 hour post-dose Day 1 of Cycle 2 and Cycle 3, and every 12 weeks thereafter (Day 1 of Cycle 6, Cycle 9 etc.) Clinical indication End of Treatment	Cycle 1 Day 1 pre-dose, and 0.5, 1.5, 4-8 hour post-dose Cycle 2 Day 1 pre-dose Cycle 3 Day 1 pre-dose

Source: Study report CP-17-006, Table 1, Page 9

Reviewer's Comment: The sponsor's timing of PK/ECG collection is acceptable, since it captures the effects near T_{max} (median ~2 h) and any potential delayed effects with multiple predose (C_{trough}) sampling.

4.2.6.5 Baseline

Last non-missing value prior to the first dose of study treatment in both reports, CP-17-005 and CP-17-006.

4.2.7 ECG Collection

See Section 4.2.6.4.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

CP-17-005 (Study CLGX818X2101): 17 and 34 patients were administered with 300 mg QD and 450 mg QD encorafenib monotherapy, respectively, in the dose expansion phase.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK, Safety	CLGX818X2101	5.3.3.2	MTD/RP2D-finding study of encorafenib in patients with <i>BRAF</i> V600-mutant locally advanced or metastatic melanoma and metastatic colorectal cancer	Phase 1 open-label study, conducted in two stages: A dose-escalation phase followed by an expansion phase with 3 separate cohorts (BRAF-naïve melanoma, BRAF-pretreated melanoma, mCRC)	Encorafenib microemulsion-based solution (30 mg/mL) and capsule (10, 25, 50, and 100 mg strengths; 50 to 700 mg QD or 75 to 150 mg BID; Oral	107 Dose-escalation phase (54 total): 4: 50 mg QD 10: 100 mg QD 6: 150 mg QD 3: 75 mg BID 4: 200 mg QD 5: 100 mg BID 5: 300 mg QD 4: 150 mg BID 6: 450 mg QD 5: 550 mg QD 2: 700 mg QD Dose-expansion phase (53 total): 9: 300 mg QD BRAF-naïve mel	Dose-escalation phase: Patients with <i>BRAF</i> V600-mutant locally advanced or metastatic melanoma (either BRAF-inhibitor naïve or BRAF-inhibitor pretreated) Expansion phase: Patients with <i>BRAF</i> V600-mutant locally advanced or metastatic	Patients treated until PD, unacceptable toxicity, physician decision, study termination or discontinuation from study treatment for any other reason (e.g., withdrawal of consent, lost to follow-up, start of a new anti-cancer therapy) + 30-day	Ongoing; Clinical Study Report on Primary Analysis
						6: 450 mg QD BRAF-naïve mel 2: 300 mg QD BRAF-pre mel 16: 450 mg QD BRAF-pre mel 2: step-wise 6: 300 mg QD mCRC 12: 450 mg QD mCRC	melanoma (either BRAF-inhibitor naïve or BRAF-inhibitor pretreated) or with <i>BRAF</i> V600-mutant mCRC	follow-up	

CP-17-006 (Pooled data from Studies CMEK162X2110, CLGX818X2109 and CMEK162B2301):

LGX818X2109: 75 patients were BRAF/MEK-treatment naïve group, and were administered with Combo 450.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy, safety	CLGX818X2109	5.3.5.2	Efficacy/safety of encorafenib plus binimetinib in combination with targeted agents	Multicenter, nonrandomized, 2-part study of sequential encorafenib/binimetinib combination followed by a rational combination with targeted agents after progression to overcome resistance	Encorafenib capsules (50 and 100 mg strengths); Per 21-day cycle: 300 mg QD; Oral Binimetinib tablet (15 mg strength); Per 21-day cycle: 45 mg BID; Oral BKM120 capsules, Per 21-day cycle: 60 mg QD; Oral BGJ398 capsules, Per 21-day cycle: 75 mg QD; Oral INC280 capsules, Per 21-day cycle: 200 mg BID; Oral LEE011 capsules Per 28-day cycle: 200 mg 3 weeks on/1 week off; Oral	Part 1 (158 total): 75: <i>BRAF</i> -inhibitor naïve 83: <i>BRAF</i> -inhibitor non-naïve	Patients with locally advanced unresectable or metastatic <i>BRAF</i> V600 melanoma	Treatment until until PD, unacceptable toxicity, withdrawal of informed consent, new therapy for study indication or death	Ongoing; Clinical Study Report on Part 1

CMEK162X2110: 13 patients in dose escalation phase were administered with Combo 450.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK, Safety, Efficacy	CMEK162X2110	5.3.3.2	MTD/RP2D-finding study of encorafenib in combination with binimetinib and in combination with binimetinib and ribociclib in patients with <i>BRAF</i> V600-dependent advanced solid tumors	Phase 1b/2, open-label study, conducted in two stages: A dose-escalation phase followed by an expansion phase with 3 separate cohorts (BRAF-naïve melanoma, BRAF-pretreated melanoma, mCRC)	Encorafenib capsules (10, 25, 50 and 100 mg strengths); Per 28-day cycle, 50 to 800 mg QD; Oral Binimetinib tablets (15 mg strength); Per 28-day cycle, 45 mg BID; Oral Ribociclib capsules 100 mg strength; QD; Oral	126 dual combination treatment (as of 31 Aug 2015) Dose-escalation phase (47 total): 6: 50 mg 5: 100 mg 4: 200 mg 5: 400 mg 13: 450 mg 8: 600 mg 6: 800 mg Expansion phase (79 total): 11: mCRC 26: prior BRAF inhibitor melanoma 42: BRAFi-naïve melanoma	Dose-escalation phase: Patients with <i>BRAF</i> V600-mutant locally advanced or metastatic melanoma, mCRC or any other <i>BRAF</i> V600-mutant solid tumor Expansion phase: Patients with <i>BRAF</i> V600-mutant mCRC or patients with locally advanced or metastatic <i>BRAF</i> V600-mutant melanoma with and without previous treatment with a selective BRAF inhibitor	Patients treated with the dual combination therapy until PD, unacceptable toxicity, physician decision, or withdrawal of consent.	Ongoing; CSR is completed on primary analysis of dual combination treatment in both study phases

CMEK162B2301: 192 subjects were administered with Combo 450.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
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Safety, efficacy	CMEK162 B2301 – Part 1	5.3.5.1	Safety and efficacy of encorafenib plus binimetinib versus vemurafenib and encorafenib monotherapy in <i>BRAF</i> V600-mutant melanoma	Phase 3, 2-part randomized, open label, multicenter study	Encorafenib capsules (50 mg strength), Binimetinib tablets (15 mg strength), Vemurafenib tablets (240 mg strength); Per 28-day cycle: encorafenib 450 mg QD plus binimetinib 45 mg BID; Oral or Encorafenib 300 mg QD; Oral or Vemurafenib 960 mg BID; Oral	Part 1 (577 total randomized): 192: Combo 450 194: encorafenib 191: vemurafenib	Patients with locally advanced unresectable or metastatic melanoma with <i>BRAF</i> V600 mutation	Patients treated PD confirmed by the BIRC, unacceptable toxicity, death, physician decision, study termination or discontinuation from study treatment for any other reason (e.g., withdrawal of consent, lost to follow-up) + 30-day follow-up	Ongoing; Clinical Study Report on Primary Analysis
Safety, efficacy	CMEK162 B2301 – Part 2	5.3.5.1	Safety and efficacy of encorafenib plus binimetinib versus encorafenib monotherapy in <i>BRAF</i> V600 mutant melanoma	Phase 3, 2-part randomized, open label, multicenter study	Encorafenib capsules (50 mg strength), binimetinib tablets (15 mg strength) Per 28-day cycle: encorafenib 300 mg QD plus binimetinib 45 mg BID; Oral or Encorafenib 300 mg QD; Oral	Part 2: (344 patients randomized): 258: Combo 300 86 encorafenib	Patients with locally advanced unresectable or metastatic melanoma with <i>BRAF</i> V600 mutation	Patients treated PD confirmed by the BIRC, unacceptable toxicity, death, physician decision, study termination or discontinuation from study treatment for any other reason (e.g., withdrawal of consent, lost to follow-up) + 30-day follow-up	Ongoing; Initial Clinical Study Report

The sample size for C-QT analysis was 107 patients for C-QT report CP-17-005 and 206 patients for C-QT report CP-17-006 based on time-matched ECG-PK data, as shown in the following table.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PopPK	CP17-005	5.3.3.5	Cardiac safety analysis of encorafenib	Time-matched ECG and encorafenib concentration data from CLGX818X2101 analyzed using linear mixed effect model	Encorafenib microemulsion-based solution (30 mg/mL) and capsule (10, 25, 50, and 100 mg strengths; QD or BID; Oral	107 patients	Patients with melanoma (either <i>BRAF</i> -inhibitor naïve or <i>BRAF</i> -inhibitor pretreated) and metastatic CRC (mCRC)	Patients treated until PD, unacceptable toxicity, physician decision, study termination or discontinuation from study treatment for any other reason (e.g., withdrawal of consent, lost to follow-up, start of a new anti-cancer therapy) + 30-day follow-up	Complete; Full
PopPK	CP17-006	5.3.3.5	Cardiac safety analysis of the encorafenib plus binimetinib combination	Pooled analysis across clinical studies CLGX818X2109 CMEK162B2301 CMEK162X2110	See individual study descriptions	206 patients	See individual study descriptions	See individual study descriptions	Complete; Full

4.2.8.2 Statistical Analyses

4.2.8.2.1 Sponsor's Analysis for Central Tendency and Categorical Analysis

Central tendency Analysis

CP-17-005 (Study CLGX818X2101)

Results for ΔQTcF are tabulated in the Sponsor's study report (Tables 8.1 – 8.8).

Reviewer's comment: The reviewer confirmed the results of these tables (See Table 6 (300 mg All and 450 mg All in reviewer's analysis).

CP-17-006 (Pooled data from Studies CMEK162X2110, CLGX818X2109 and CMEK162B2301)

Results for Δ QTcF are tabulated in the Sponsor's study report (Tables 8.1.1 and 8.1.2).

Reviewer's comment: The reviewer confirmed the results of Sponsor's tables, including Tables 8.1.1 and 8.1.2 and generated analysis by each study (see Table 7 in reviewer's analysis).

Categorical Analysis

The sponsor's analysis presented ECG results from pooled data for subjects treated with Combo 450 treatment (450 mg QD of encorafenib in combination with binimetinib 45 mg BID) and single-agent encorafenib 300 mg QD treatment based on following two safety sets in melanoma population. The results of sponsor's pooled categorical analysis are presented in Table 3 below.

The Restricted Combination Set (for Combo 450 treatment): includes pooled combination safety data from 3 clinical studies (CMEK162B2301 Part 1, CLGX818X2109 and CMEK162X2110). The population included in the Restricted Combination Safety Set corresponds to patients with metastatic melanoma who were previously naïve to BRAF/MEK inhibitors, treated at the recommended combination dose of encorafenib 450 mg QD plus binimetinib 45 mg BID (274 total patients).

The Encorafenib Monotherapy Safety Set: includes pooled single-agent encorafenib safety data from 3 clinical studies (CMEK162B2301 Part 1, CMEK162X2102 and CLGX818X2101). The population included in the Encorafenib Monotherapy Safety Set corresponds to patients with metastatic melanoma, who were previously naïve to BRAF inhibitors, treated with encorafenib 300 mg QD (217 total patients).

Table 3: Patients with Newly Occurring Notable ECG Values by Treatment (Restricted Safety Set, Part 1)

Vital Sign Category	Melanoma			Study CMEK162B2301 Part 1		
	Binimetinib 45 mg BID N=427 n/m (%)	Encorafenib 300 mg QD N=217 n/m (%)	Combo 450 mg QD N=274 n/m (%)	Combo 450 mg QD N=192 n/m (%)	Encorafenib 300 mg QD N=192 n/m (%)	Vemurafenib N=186 n/m (%)
QTcF (ms)						
Increase from baseline > 30 ms	82/412 (19.9)	65/204 (31.9)	98/268 (36.6)	50/186 (26.9)	52/179 (29.1)	76/179 (42.5)
Increase from baseline > 60 ms	11/412 (2.7)	7/204 (3.4)	13/268 (4.9)	10/186 (5.4)	7/179 (3.9)	10/179 (5.6)
New > 450 ms	51/384 (13.3)	44/194 (22.7)	50/259 (19.3)	25/178 (14.0)	36/171 (21.1)	42/174 (24.1)
New > 480 ms	15/411 (3.6)	10/202 (5.0)	11/268 (4.1)	7/186 (3.8)	7/177 (4.0)	5/179 (2.8)
New > 500 ms	5/412 (1.2)	5/203 (2.5)	2/268 (0.7)	1/186 (0.5)	5/178 (2.8)	3/179 (1.7)

Newly occurring: Patients not meeting criterion at baseline and meeting criterion post-baseline.

n: Number of patients who meet the criteria at least once.

m: Number of patients at risk, i.e., with a non-missing value at baseline and post-baseline, and with a baseline value that does not already meet the abnormality, which is used to calculate the percentage.

N: Total number of patients in the treatment group in this analysis set.

All scheduled and unscheduled visits are included in this output.

Source: Table 4-2, page 382 of 29053 of [ISS](#)

Reviewer's comment: The reviewer confirmed the results for the Combo 450 (450 mg QD Encorafenib + 45 mg BID Binimetinib) regimen (see Table 8 in reviewer's analysis).

4.2.8.2.2 Assay Sensitivity

Not applicable.

4.2.8.3 Safety Analysis

The sponsor searched the clinical database for events of torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation, ventricular flutter, syncope and seizures using the MedDRA version 18.1 Standardized MedDRA Queries (SMQs) Torsade de pointes/QT prolongation (broad), Ventricular tachyarrhythmias (narrow) and Convulsions (narrow). The results are presented in Appendix 6.3 Clinical Cardiac Safety.

Reviewer's comment: The sponsor did not summarize these data in a format that allows for easy interpretation. Nonetheless, the AEs do not appear to be related to QTc prolongation.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The T_{max} of encorafenib when administered alone were similar across the doses studied in Study CLGX818X2101, with median of 1.5 to 2.0 hours. The dose proportionality evaluation suggested that encorafenib AUC_{inf} and C_{max} were approximately dose proportional over the dose range of 50 to 700 mg following a single dose and over the dose range of 50 to 550 mg at steady state (Day 15). The accumulation ratio of AUC (R_{AUC}) of encorafenib was below 1 across all dose ranges (0.401 to 0.541).

The pharmacokinetic profile of encorafenib and binimetinib in the combination therapy was evaluated in study CMEK162X2110. PK parameters after single dose and repeat-dose administration are summarized in Table 4 and Table 5.

Table 4: Summary of PK Parameters for Encorafenib in Study CMEK162X2110

Study Day	Encorafenib Dose Level ^a	AUC_{inf} (h*ng/mL)	AUC_{last} (h*ng/mL)	AUC_{tau} (h*ng/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)
Cycle 1 Day 1	50 mg (N=6)	2910 (106.1)	2830 (112.0)	2890 (105.4)	704 (88.1)	3.63 (19.2)
	100 mg (N=5)	10500 (55.2)	10400 (54.9)	10400 (54.9)	1850 (32.7)	3.64 (9.9)
	200 mg (N=4)	20600 (42.9)	20500 (42.9)	20500 (42.9)	3580 (43.6)	2.88 (4.2)
	400 mg (N=5)	36700 (68.4)	35500 (64.3)	35500 (64.3)	6740 (26.7)	3.87 (45.5)
	450 mg (N=13)	32400 (54.1)	31800 (55.8)	32200 (53.7)	7040 (41.7)	3.45 (11.2)
	600 mg (N=8)	52600 (46.7)	52200 (46.5)	52200 (46.5)	9880 (31.8)	3.18 (16.4)
	800 mg (N=6)	34500 (42.2)	33200 (38.3)	34300 (42.2)	5840 (57.5)	3.04 (3.1)
Study Day	Treatment ^a /Arm	$AUC_{last,ss}$ (h*ng/mL)	$AUC_{tau,ss}$ (h*ng/mL)	$C_{max,ss}$ (ng/mL)	$t_{1/2,ss}$ (h)	RA
Cycle 1 Day 15	50 mg (N=6)	2340 (59.2)	2340 (59.2)	498 (75.5)	4.63 (24.7)	0.811 (35.7)
	100 mg (N=5)	5370 (27.0)	5370 (27.0)	1140 (34.1)	4.45 (8.7)	0.518 (72.4)
	200 mg (N=4)	4470 (37.5)	4470 (37.5)	1050 (18.5)	4.23 (30.0)	0.294 (23.4)
	400 mg (N=5)	10100 (21.4)	10100 (21.4)	3610 (35.2)	4.17 (17.4)	0.331 (41.8)
	450 mg (N=13)	13900 (58.9)	13900 (58.9)	3760 (62.6)	3.52 (17.1)	0.421 (47.4)
	600 mg (N=8)	23200 (68.9)	23200 (68.9)	6970 (123.1)	3.39 (6.6)	0.426 (56.5)
	800 mg (N=6)	17000 (103.1)	23800 (28.0)	6110 (46.7)	3.24 (14.7)	0.736 (14.5)

Geo-mean (CV% geo-mean) values were reported for the parameters.

^aThe dual combination treatment had a fixed dose of binimetinib at 45 mg BID for all encorafenib dose levels.

Source: Study Report CMEK162X2110, Table 12, Page 116

Table 5: Summary of PK Parameters for Binimetinib in Study CMEK162X2110

Study Day	Encorafenib Dose Level ^a	AUC _{inf} (h*ng/mL)	AUC _{last} (h*ng/mL)	AUC _{tau} (h*ng/mL)	C _{max} (ng/mL)	t _{1/2} (h)
Cycle 1 Day 1	50 mg (N=6)	1850 (73.6)	1720 (66.9)	1790 (74.7)	527 (78.9)	2.33 (17.5)
	100 mg (N=5)	1880 (28.6)	1890 (37.6)	1810 (29.5)	572 (25.8)	2.29 (29.7)
	200 mg (N=4)	3070 (103.6)	2740 (99.4)	2970 (101.5)	770 (112.5)	2.06 (25.8)
	400 mg (N=5)	1770 (57.7)	1720 (49.7)	1700 (57.8)	493 (48.9)	2.48 (18.6)
	450 mg (N=13)	2470 (49.3)	2110 (47.2)	2390 (48.2)	735 (45.4)	2.18 (20.3)
	600 mg (N=8)	2800 (49.3)	2530 (48.5)	2730 (49.1)	821 (46.1)	2.10 (14.0)
	800 mg (N=6)	2310 (18.9)	2080 (21.5)	2240 (20.0)	605 (26.8)	1.92 (31.5)
Study Day	Treatment ^a /Arm	AUC _{last,ss} (h*ng/mL)	AUC _{tau,ss} (h*ng/mL)	C _{max,ss} (ng/mL)	t _{1/2,ss} (h)	RA
Cycle 1 Day 15	50 mg (N=6)	2690 (50.0)	2690 (50.0)	648 (40.9)	4.63 (31.4)	1.50 (16.8)
	100 mg (N=5)	2480 (37.7)	2480 (37.7)	526 (48.9)	4.65 (30.1)	1.25 (12.3)
	200 mg (N=4)	2300 (92.2)	2300 (92.2)	532 (92.0)	3.28 (NE)	1.06 (13.4)
	400 mg (N=5)	1880 (59.0)	1880 (59.0)	464 (84.9)	4.01 (38.8)	0.938 (40.1)
	450 mg (N=13)	2420 (33.9)	2420 (33.9)	595 (39.0)	3.48 (28.5)	0.987 (32.0)
	600 mg (N=8)	2210 (67.9)	2210 (67.9)	651 (52.1)	NE (NE)	0.928 (34.4)
	800 mg (N=6)	2500 (20.2)	2500 (20.2)	705 (27.5)	2.91 (5.3)	1.13 (36.7)

Geo-mean (CV% geo-mean) values were reported for the parameters. NE: not estimable.

^a The dual combination treatment had a fixed dose of binimetinib at 45 mg BID for all encorafenib dose levels..

Source: Study Report CMEK162X2110, Table 13, Page 117

4.2.8.4.2 Exposure-Response Analysis

Reviewer's Comment: The sponsor performed the C-QTc analyses in both study reports CP-17-005 and CP-17-006. But, the data are not amenable for C-QTc analysis due to the lack of direct relationship between concentration of encorafenib and QTc effects (i.e. time delay observed between maximum peak encorafenib concentration and maximum peak ΔQTc; see Section 5.3).

5 REVIEWERS' ASSESSMENT

The reviewers evaluated and presented the data from multiple studies (Studies CLGX818X2101, CLGX818X2109, CMEK162B2301, and CMEK162X2110) in this review for the following reasons:

1. Following general observations were made based on the results from pooled data from multiple studies:

- ECG assessments at T_{max} after multiple dosing showed higher ΔQTc compared to that at T_{max} after first dose.
- ΔQTc at C_{trough,ss} was much smaller compared to ΔQTc at C_{max,ss} (C_{max,ss} >> C_{trough,ss})

2. Study CLGX818X2101 was the only study where there was data for both 300 and 450 mg QD encorafenib monotherapy. This data was useful to conclude about dose-dependent QTc effects using the central tendency analysis.

3. Study CLGX818X2109 had studied Combo 450 regimen and had multiple post-dose (near T_{max}) planned ECG assessments (after first dose, and at Week 2, Week 4, Week 6 etc.). Thus, this study was useful to quantify the maximum mean QTc effects for Combo 450 regimen using central tendency analysis. This study also contributed towards quantifying outlier QTc values corresponding to scheduled and unscheduled visits in the pooled analysis for Combo 450 regimen.

4. The pivotal Study CMEK162B2301 had studied Combo 450 regimen and 300 mg QD encorafenib monotherapy regimen, but it did not have 450 mg QD monotherapy regimen. Furthermore, the planned ECG assessments in this study were only pre-dose trough values at multiple visits except post-dose after 1st dose. So, this study is not informative from the perspective of central tendency analysis. The study contributed towards quantifying outlier QTc values corresponding to scheduled and unscheduled visits in the pooled analysis for Combo 450 regimen.

5. Study CMEK162X2110 had studied Combo 450 regimen, but the planned ECG assessments in this study were only pre-dose trough values at multiple visits. So, this study is not informative from the perspective of central tendency analysis. The study contributed towards quantifying outlier QTc values corresponding to scheduled and unscheduled visits in the pooled analysis for Combo 450 regimen.

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

QTcF was used for the primary statistical analysis and other analyses. There were no significant mean heart rate effects (>10 bpm) with the drug as seen from analysis in Section 5.2.2.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 Central Tendency Analysis

CP-17-005 (Study CLGX818X2101 Expansion Phase): A descriptive comparison was made between pre-dose baseline and post dose for all populations (melanoma-naïve and pretreated and mCRC) combined by dose groups (Table 6).

Table 6: Central tendency analysis for Δ QTcF for Encorafenib monotherapy (Study CLGX818X2101 Expansion Phase): By Dose Groups

Dose Group	Analysis Visit	Time	Number of Obs.	Δ QTcF MEAN (SD)	Δ QTcF 90% CI
300 mg All (n=17)	Day 1	2 h post-dose	16	5.2 (9.04)	(1.2, 9.2)
	Day 15	2 h post-dose	11	12.9 (11.05)	(6.9, 18.9)
450 mg All (n=34)	Day 1	0.5 h post-dose	23	3.2 (9.96)	(-0.4, 6.8)
	Day 1	2 h post-dose	31	12.6 (11.52)	(9.1, 16.1)
	Day 1	6 h post-dose	21	8.0 (12.66)	(3.2, 12.7)
	Day 1	24 h post-dose	20	8.2 (18.1)	(1.2, 15.2)
	Day 15	0.5 h post-dose	18	9.7 (16.59)	(2.9, 16.5)
	Day 15	2 h post-dose	19	19.9 (16.59)	(13.3, 26.5)
	Day 15	6 h post-dose	19	11.2 (15.97)	(4.9, 17.6)
	Day 15	24 h post-dose	24	6.5 (15.12)	(1.2, 11.7)

Note: The Sponsor defined Baseline as the last non-missing value prior to the first dose of study treatment. (See Table 1 of the Sponsor's report (pages 11-12). Some timepoints (e.g. Day 1- 6 and 24 h timepoint in 300 mg All) are not shown because of too small sample sizes (n~4-6) to get precise estimates.

CP-17-006 (Pooled data from Studies CLGX818X2109, CMEK162B2301, CMEK162X2110): A descriptive comparison was made between pre-dose baseline and post dose timepoints for the pooled data. Analyses are presented by individual study because only the Study CLGX818X2109 had scheduled ECG assessments at multiple post-dose T_{max} timepoints, while other two studies had scheduled ECG assessments at just multiple predose (trough) timepoints.

Table 7: Central tendency analysis for Δ QTcF for Combo 450: By study

Study	Analysis Visit	#Subjects with ECG data (Total Number of Subjects)	Δ QTcF MEAN (SD)	Δ QTcF 90% CI
CLGX818X2109	Baseline	75 (75)		

Study	Analysis Visit	#Subjects with ECG data (Total Number of Subjects)	Δ QTcF MEAN (SD)	Δ QTcF 90% CI
	Week 0 Post dose	67	5.7 (10.70)	(3.5, 7.9)
	Week 2 Post dose	67	13.7 (14.57)	(10.7, 16.6)
	Week 4 Post dose	70	13.5 (15.85)	(10.3, 16.6)
	Week 6 Post dose	66	18.3 (18.73)	(14.4, 22.1)
	Week 8 Post dose	71	15.8 (21.53)	(11.5, 20.0)
CMEK162B2301	Baseline	188 (192)		
	Week 0 Post dose	149	2.1 (16.03)	(-0.1, 4.3)
	Week 2 Pre-dose	3	2.3 (21.03)	(-33.2, 37.7)
	Week 4 Pre-dose	169	4.0 (22.18)	(1.1, 6.8)
	Week 6 Pre-dose	6	4.0 (23.19)	(-15.0, 23.1)
	Week 8 Pre-dose	174	7.3 (22.14)	(4.5, 10.0)
CMEK162X2110	Baseline	7 (13)		
	Week 2 Pre-dose	5	9.4 (8.15)	(1.6, 17.2)
	Week 4 Pre-dose	6	8.3 (12.25)	(-1.7, 18.4)
	Week 6 Pre-dose	7	13.0 (14.74)	(2.2, 23.8)
	Week 8 Pre-dose	7	12.4 (14.19)	(2.0, 22.9)

Note: The Sponsor defined Baseline as the last non-missing value prior to the first dose of study treatment. The “Post-dose” data were measured at 1.5 hour post-dose time point of Day 1 at each preplanned week.

5.2.1.2 Assay Sensitivity Analysis

Not applicable.

5.2.1.3 Categorical Analysis (QTcF and Δ QTcF)

Categorical (outlier) analysis for the Combo 450 (450 mg QD Encorafenib + 45 mg BID Binimetinib) regimen is based on QTc data from all visits (scheduled and unscheduled) in pooled Studies CLGX818X2109, CMEK162X2110, and CMEK162B2301 in patients (based on original adecg.xpt dataset submitted by the sponsor). The results from the reviewer’s analysis (Table 8) match with the sponsor’s analysis and these results are used in the proposed labeling for Section 12.2. Because Study CLGX818X2109 had scheduled ECG assessments at multiple post-dose T_{max} timepoints, while other two studies had scheduled ECG assessments at just multiple predose (trough) timepoints, the data from this study alone is evaluated as a sensitivity analysis for data from pooled studies. The data from Study CLGX818X2109 alone showed similar percentage of outliers as that of the data from pooled studies for categories of QTcF >500 ms and Δ QTcF >60 ms.

Table 8: Categorical Analysis for Newly Occurring Notable QTcF and Δ QTcF for Combo 450 regimen (Safety Population)

	Pooled Studies CLGX818X2109, CMEK162X2110, and CMEK162B2301 (N=274)	Study CLGX818X2109 alone (N=75)
	Combo 450 (450 mg QD Encorafenib + 45 mg BID Binimetinib) n/m (%)	
Newly Occurring Notable QTcF		
> 450 ms	50/259 (19.3)	22/74 (29.7)
> 480 ms	11/268 (4.1)	4/75 (5.3)
> 500 ms	2/268 (0.7)	1/75 (1.3)
ΔQTcF		
> 30 ms	98/268 (36.6)	45/75 (60.0)

> 60 ms	13/268 (4.9)	3/75 (4.0)
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Newly occurring: Patients not meeting criterion at baseline and meeting criterion at post-baseline time.
All scheduled and unscheduled visits are included in this output.

n: Number of patients who meet the criteria at least once.

m: Number of patients at risk, i.e., with non-missing values at baseline and post-baseline, and with a baseline value that does not already meet the abnormality, which is used to calculate the percentage.

N: Total number of patients in the treatment group in this analysis set.

ΔQTcF: Change from baseline in QTcF

5.2.2 HR Analysis

The descriptive analysis results, and categorical analysis results are provided for Heart Rate (HR) and the change from baseline in HR (ΔHR) for encorafenib monotherapy and Combo 450 regimen. The categorical analyses show that a substantial number of subjects had an increase in HR (ΔHR >20 bpm) with encorafenib monotherapy, though the central tendency analysis at two T_{max} timepoints (Day 1 and Day 15) do not show mean ΔHR effects >10 bpm. The heart rate effect was much less pronounced with Combo 450 regimen (comparing the category of ΔHR >20 bpm).

Table 9: Central tendency analysis for ΔHR for Encorafenib monotherapy (Study CLGX818X2101 Expansion Phase): By Dose Groups

Dose Group	Analysis Visit	Time	Number of Obs.	HR MEAN (SD)	HR 90% CI	ΔHR MEAN (SD)	ΔHR 90% CI
300 mg All	Baseline	0 (pre-dose)	17	76.6 (10.8)	(72.0, 81.1)		
	Day 1	2	16	72.9 (12.52)	(67.4, 78.4)	-3.1 (7.86)	(-6.5, 0.3)
	Day 15	0 (pre-dose)	13	85.2 (10.95)	(79.8, 90.6)		
		2	11	77.3 (13.29)	(70.1, 84.6)	2.4 (13.21)	(-4.8, 9.6)
450 mg All	Baseline	0 (pre-dose)	34	73.8 (11.27)	(70.5, 77.0)		
	Day 1	2	31	71.4 (9.3)	(68.6, 74.3)	-2.6 (6.14)	(-4.5, -0.7)
	Day 15	0 (pre-dose)	28	78.7 (10.98)	(75.1, 82.2)		
		2	19	80.1 (8.59)	(76.7, 83.5)	5.1 (8.82)	(1.6, 8.6)

Note: The Sponsor defined Baseline as the last non-missing value prior to the first dose of study treatment. The displayed data at Time (Hour) > 0 are all post dose. In the Sponsor's report, Cycle 1 Day 1 Hour 2 and Cycle 1 Day 15 Hour 2 results are listed. All displayed data are based on Cycle 1 available QT data (See Table 1 of the Sponsor's report (pages 11-12)).

Table 10: Categorical Analysis for HR and ΔHR for Encorafenib monotherapy (Study CLGX818X2101 Expansion Phase): By Dose Groups

Dose Group (N: Total #Subjects)	Baseline #Subjects with (HR>100bpm) / #Observed Subjects (%)	Post-baseline (all visits) #Subjects with (HR>100bpm) / #Observed Subjects (%)
300 mg All (N=17)	1/17 (5.9)	4/17 (23.5)
450 mg All (N=34)	1/34 (0.0)	8/34 (23.5)

Dose Group (N: Total #Subjects)	Post-baseline (all visits)	
	#Subjects with (ΔHR>20bpm) / #Observed Subjects (%)	#Subjects with (ΔHR>30bpm) / #Observed Subjects (%)
300 mg All (N=17)	8/17 (47.1)	2/17 (11.8)
450 mg All (N=34)	13/34 (38.2)	3/34 (8.2)

Note: Post-baseline visits include unscheduled visits.

Table 11: Central tendency analysis for ΔHR for Combo 450: By study

Study	Analysis Visit	#Subjects with ECG data (Total Number of Subjects)	HR MEAN (SD)	HR 90% CI	ΔHR MEAN (SD)	ΔHR 90% CI
CLGX818X2109	Baseline	73	72.8 (10.66)	(70.7, 74.9)		

Study	Analysis Visit	#Subjects with ECG data (Total Number of Subjects)	HR MEAN (SD)	HR 90% CI	ΔHR MEAN (SD)	ΔHR 90% CI
CMEK162B2301	Week 0 Post dose	66	70.8 (10.46)	(68.7, 73.0)	-1.6 (5.95)	(-2.9, -0.4)
	Week 2 Post dose	65	68.9 (12.72)	(66.2, 71.5)	-4.1 (12.55)	(-6.7, -1.5)
	Week 4 Post dose	68	66.8 (9.11)	(65.0, 68.7)	-5.6 (11.00)	(-7.9, -3.4)
	Week 6 Post dose	64	66.7 (9.39)	(64.7, 68.6)	-5.9 (11.64)	(-8.3, -3.4)
	Week 8 Post dose	69	67.8 (9.56)	(65.9, 69.7)	-4.6 (11.12)	(-6.8, -2.4)
	Baseline	189	74.9 (12.91)	(73.3, 76.5)		
	Week 0 Post dose	150	74.2 (12.37)	(72.6, 75.9)	-0.8 (8.37)	(-1.9, 0.4)
	Week 2 Pre-dose	3	81 (12.53)	(59.9, 102.1)	-11.8 (9.79)	(-28.3, 4.7)
	Week 4 Pre-dose	171	70.0 (12.23)	(68.4, 71.5)	-4.6 (11.78)	(-6.1, -3.1)
	Week 6 Pre-dose	6	80.7 (8.85)	(73.4, 87.9)	-7.5 (12.59)	(-17.9, 2.8)
CMEK162X2110	Week 8 Pre-dose	175	70.6 (12.66)	(69.0, 72.2)	-4.3 (12.07)	(-5.8, -2.8)
	Baseline	7	67.9 (14.04)	(57.5, 78.2)		
	Week 2 Pre-dose	5	62.8 (14.55)	(48.9, 76.7)	-5.0 (7.34)	(-12, 2.0)
	Week 4 Pre-dose	6	67.8 (13.39)	(56.8, 78.9)	0.9 (8.4)	(-6.0, 7.8)
	Week 6 Pre-dose	7	72.1 (15.06)	(61.1, 83.2)	4.3 (7.78)	(-1.4, 10.0)
	Week 8 Pre-dose	7	72.0 (11.69)	(63.4, 80.6)	4.1 (8.18)	(-1.9, 10.2)

Note: The Sponsor defined Baseline as the last non-missing value prior to the first dose of study treatment. The “Post dose” data were measured at 1.5 hour post-dose time point of Day 1 at each preplanned week. SD denotes standard deviation.

Table 12: Categorical Analysis for HR and ΔHR for the Combo 450 regimen (450 mg QD Encorafenib + 45 mg BID Binimetinib): By Study

Study	Baseline #Subjects with (HR>100bpm) / #Observed Subjects (%)	Post First Dosing (all visits) #Subjects with (HR>100bpm) / #Observed Subjects (%)
CLGX818X2109 (N=75)	0/75 (0.0)	6/75 (8.0)
CMEK162B2301 (N=192)	5/192 (2.6)	19/190 (10.0)
CMEK162X2110 (N=7)	0/7 (0.0)	1/7 (14.3)

Study (N: #Subjects with HR records)	Post First Dosing (all visits) #Subjects with (ΔHR>20bpm) / #Observed Subjects (%)	#Subjects with (ΔHR >30 bpm) / #Observed Subjects (%)
CLGX818X2109 (N=75)	15/75 (20.0)	5/75 (6.7)
CMEK162B2301 (N=192)	28/190 (14.7)	6/190 (3.2)
CMEK162X2110 (N=7)	2/7 (28.6)	2/7 (28.6)

Note: Post-baseline visits include unscheduled visits.

5.2.3 PR Analysis

In this section, descriptive summary and categorical analysis results, are provided for PR interval for encorafenib monotherapy and Combo 450 regimen. There is some increase in PR interval seen with Combo 450 regimen with both descriptive and categorical analyses.

Table 13: Central tendency analysis for ΔPR for Encorafenib monotherapy (Study CLGX818X2101 Expansion Phase): By Dose Groups

Dose Group	Analysis Visit	Time	Number of Obs.	ΔPR MEAN (SD)	ΔPR 90% CI
300 mg All	Baseline	0 (pre-dose)	17		
	Day 1	2 h post-dose	16	-0.8 (8.98)	(-4.7, 3.2)
	Day 15	2 h post-dose	11	-4.4 (10.7)	(-10.2, 1.5)
450 mg All	Baseline	0 (pre-dose)	34		

Dose Group	Analysis Visit	Time	Number of Obs.	ΔPR MEAN (SD)	ΔPR 90% CI
	Day 1	2 h post-dose	31	-1.2 (7.56)	(-3.5, 1.1)
	Day 15	2 h post-dose	19	-3.7 (8.06)	(-6.9, -0.5)

Note: The Sponsor defined Baseline as the last non-missing value prior to the first dose of study treatment. The displayed data at Time (Hour) > 0 are all post dose. In the Sponsor's report, Cycle 1 Day 1 Hour 2 and Cycle 1 Day 15 Hour 2 results are listed, which is the sum of numbers of subjects at baseline of all dose groups in the table (See Table 1 of the Sponsor's report (pages 11-12)).

Table 14: Categorical Analysis for PR for Encorafenib monotherapy (Study CLGX818X2101 Expansion Phase): By Dose Groups

Dose Group (N: Total #Subjects)	Baseline #Subjects with (PR>200ms) / #Observed Subjects (%)	Post-baseline (all visits) #Subject with (PR>200ms) / #Observed Subjects (%)
300 mg All (N=17)	0/17 (0.0)	2/17 (11.8)
450 mg All (N=34)	0/33 (0.0)	2/34 (5.9)

Note: Post-baseline visits include unscheduled visits.

Table 15: Central tendency analysis for ΔPR for Combo 450: By study

Study	Analysis Visit	#Subjects with ECG data (Total Number of Subjects)	ΔPR MEAN (SD)	ΔPR 90% CI
CLGX818X2109	Baseline	73		
	Week 0 Post dose	64	1.2 (8.06)	(-0.5, 2.9)
	Week 2 Post dose	64	5.9 (14.24)	(2.9, 8.8)
	Week 4 Post dose	67	6.2 (15.03)	(3.2, 9.3)
	Week 6 Post dose	63	6.3 (17.40)	(2.6, 9.9)
	Week 8 Post dose	68	6.8 (15.65)	(3.7, 10.0)
CMEK162B2301	Baseline	96		
	Week 0 Post dose	66	0.7 (17.38)	(-2.9, 4.2)
	Week 2 Pre-dose	2	-14.5 (26.16)	(-131.3, 102.3)
	Week 4 Pre-dose	69	0.6 (19.19)	(-3.2, 4.5)
	Week 6 Pre-dose	3	9.6 (17.39)	(-19.8, 38.9)
	Week 8 Pre-dose	78	9.3 (60.44)	(-2.1, 20.7)
CMEK162X2110	Baseline	7		
	Week 2 Pre-dose	5	-0.7 (6.87)	(-7.3, 5.8)
	Week 4 Pre-dose	6	-1.1 (6.56)	(-6.4, 4.3)
	Week 6 Pre-dose	7	2.3 (10.53)	(-5.4, 10.1)
	Week 8 Pre-dose	7	4.5 (6.90)	(-0.6, 9.5)

Note: The Sponsor defined Baseline as the last non-missing value prior to the first dose of study treatment. The "Post dose" data were measured at 1.5 hour post-dose time point of Day 1 at each preplanned week. SD denotes standard deviation.

Table 16: Categorical Analysis for PR for Combo 450 (450 mg QD Encorafenib + 45 mg BID Binimetinib) regimen: By Study

Study (N: #Subjects with PR records)	Baseline #Subjects with (PR>200ms) / #Observed Subjects (%)	Baseline #Subjects with (PR>220ms) / #Observed Subjects (%)	Post First Dosing (all visits) #Subjects with (PR>200ms) / #Observed Subjects (%)	Post First Dosing (all visits) #Subjects with (PR>220ms) / #Observed Subjects (%)
CLGX818X2109 (N=75)	6/74 (8.1)	1/74 (1.4)	26/73 (35.6)	7/73 (9.6)
CMEK162B2301(N=192)	5/177 (2.8)	4/177 (2.3)	24/175 (13.7)	10/175 (5.7)
CMEK162X2110 (N=7)	0/7 (0.0)	0/7 (0.0)	2/7 (28.6)	1/7 (14.3)

Note: Post-baseline visits include unscheduled visits.

5.2.4 QRS Analysis

In this section, descriptive summary and categorical analysis results, are provided for QRS interval for encorafenib monotherapy and Combo 450 regimen. The results do not show any sign of an increase in QRS.

Table 17: Central tendency analysis for Δ QRS for Encorafenib monotherapy (Study CLGX818X2101 Expansion Phase): By Dose Groups

Dose Group	Analysis Visit	Time	Number of Obs.	Δ QRS MEAN (SD)	Δ QRS 90% CI
300 mg All	Baseline	0 (pre-dose)	17		
	Day 1	2 h post-dose	16	1.4 (4.59)	(-0.6, 3.4)
	Day 15	2 h post-dose	11	-0.6 (4.56)	(-3.1, 1.9)
450 mg All	Baseline	0 (pre-dose)	34		
	Day 1	2 h post-dose	31	-0.1 (5.52)	(-1.8, 1.6)
	Day 15	2 h post-dose	19	-0.1 (5.58)	(-2.3, 2.2)

Note: The Sponsor defined Baseline as the last non-missing value prior to the first dose of study treatment. The displayed data at Time (Hour) = 2 are all post dose. In the Sponsor's report, Cycle 1 Day 1 Hour 2 and Cycle 1 Day 15 Hour 2 results are listed. All data displayed above are based on Cycle 1 baseline and Hour 2 QRS data (See Table 1 of the Sponsor's report (pages 11-12)).

Table 18: Categorical Analysis for QRS for Encorafenib monotherapy (Study CLGX818X2101 Expansion Phase): By Dose Groups

Dose Group (N: Total #Subjects)	Baseline #Subjects with (QRS>110ms) / #Observed Subjects (%)	Post-baseline (all visits) #Subjects with (QRS>110ms) / #Observed Subjects (%)
300 mg All (N=17)	1/17 (5.9)	1/17 (5.9)
450 mg All (N=34)	0/34 (0.0)	1/34 (2.9)

Note: Post-baseline visits include unscheduled visits.

Table 19: Central tendency analysis for Δ QRS for Combo 450: By study

Study	Analysis Visit	#Subjects with ECG data (Total Number of Subjects)	Δ QRS MEAN (SD)	Δ QRS 90% CI
CLGX818X2109	Baseline	75		
	Week 0 Post dose	67	-0.3 (5.07)	(-1.4, 0.7)
	Week 2 Post dose	67	0.6 (7.15)	(-0.9, 2.0)
	Week 4 Post dose	70	1.0 (6.01)	(-0.2, 2.2)
	Week 6 Post dose	66	1.4 (9.42)	(-0.5, 3.3)
	Week 8 Post dose	71	1.0 (6.96)	(-0.4, 2.3)
CMEK162X2110	Baseline	7		
	Week 2 Pre-dose	5	-1.3 (5.72)	(-6.7, 4.2)
	Week 4 Pre-dose	6	-0.3 (5.05)	(-4.4, 3.9)
	Week 6 Pre-dose	7	-0.9 (9.01)	(-7.5, 5.7)
	Week 8 Pre-dose	7	-1.3 (5.00)	(-5.0, 2.3)

Note: The Sponsor defined Baseline as the last non-missing value prior to the first dose of study treatment. The "Post dose" data were measured at 1.5 hour post-dose time point of Day 1 at each preplanned week. QRS duration data is not available for Study CMEK162B2301.

Table 20: Categorical Analysis for QRS for Combo 450: By Study

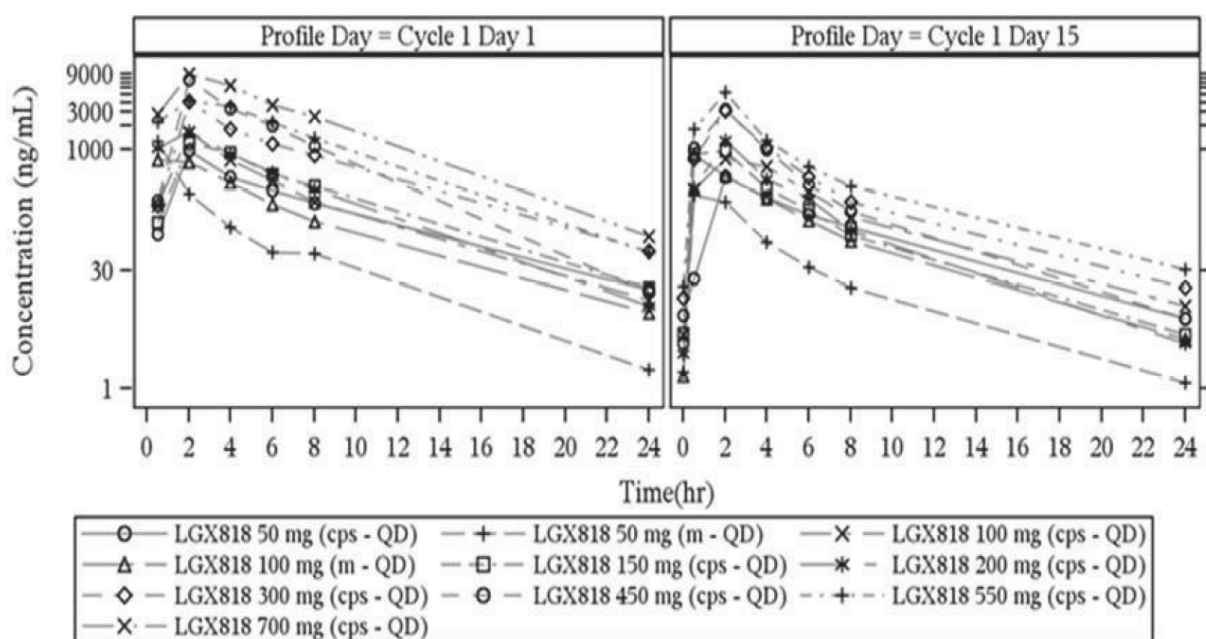
Study (N: #Subjects with QRS records)	Baseline #Subjects with (QRS>110ms) / #Observed Subjects (%)	Post First Dosing (all visits) #Subjects with (QRS>110ms) / #Observed Subjects (%)
CLGX818X2109 (N=75)	4/75 (5.3)	15/75 (20.0)
CMEK162X2110 (N=7)	1/7 (14.3)	2/7 (28.6)

Reference ID: 4193570 Note: QRS was not obtained in Study CMEK162B2301. Post-baseline visits include unscheduled visits.

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The median encorafenib concentration-time profile after a single dose and at steady state as a single agent are illustrated in Figure 1. It is evident that the maximum $C_{\max}$ is attained after the first dose and thereafter the $C_{\max}$ are lower with multiple dosing. Unlike this, the information from Table 6 and Table 7 clearly shows that there is a temporal increase in QTc effects (higher post-dose Δ QTc after ≥ 2 weeks of dosing compared to post-dose Δ QTc on Day 1). Thus, there is a lack of direct relationship between concentrations of encorafenib and QTc effects and a linear C-QTc model cannot be used for analysis to predict the effects. The C-QTc analysis was not conducted and instead the results from the statistical assessments described in Section 5.2 are used for our overall conclusion.

Figure 1: Median semi-logarithmic concentration-time profiles for plasma concentration of encorafenib by time and treatment group (PAS, dose escalation phase, once daily regimen)



Source: Study Report CLGX818X2101, Figure 11-7, Page 127

5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

See Appendix 6.3 Clinical Cardiac Safety for analysis of AEs that are important to ICH E14 guidelines. None of the AEs appear to be directly related to QTc prolongation.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in three studies (CLGX818X2101, CLGX818X2109, and CMEK162X2110) appears acceptable.

ECGs from Study CMEK162B2301 have not been submitted to the ECG warehouse yet. The sponsor's response to our information request in August 2017 states, "ECGs from Study CMEK162B2301 included in the restricted safety set will be collected from sites and digitized, and submitted to the ECG warehouse. Current estimates to complete this activity are 3-4 months."

5.4.3 PR and QRS Interval

There is no evidence that encorafenib prolongs the QRS interval.

The PR interval is slightly increased (largest mean change is around 10 ms) with encorafenib treatment. In study CMEK162B2301, 10 (5.7%) patients had a PR interval >220 ms.

Ascribing clinical meaningfulness to lower degrees of AV block is not clear and the IRT has not been recommending labeling for mild increases in PR interval.

7 APPENDIX

7.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure	Maximum proposed clinical dosing regimen from the single-agent dose-escalation study [CLGX818X2101] in cancer patients with locally advanced or metastatic BRAF mutant melanoma: 300 mg QD Single dose mean (%CV) C_{max}: 3520 ng/mL (35.8%) Single dose mean (%CV) AUC_{inf}: 20,800 h*ng/mL (30.3%) Steady state (Day 15) mean (%CV) C_{max}: 3040 ng/mL (30.5%) Steady state (Day 15) mean (%CV) AUC_{tau}: 11,000 h*ng/mL (38.6%) Preliminary data for encorafenib 450 mg (in combination with binimetinib 45 mg): Single dose mean C_{max}: 7622 ng/mL Single dose mean AUC_{tau}: 39,342 h*ng/mL Steady state mean C_{max} (Day 15): 4338 ng/mL Steady state mean AUC_{tau} (Day 15): 16,083 h*ng/mL	
Maximum tolerated dose	300 mg QD as a single agent, 450 mg QD in combination with 45 mg Binimetinib	
Principal adverse events	The most common AEs ($\geq 20\%$) suspected to be related to encorafenib single-agent treatment, regardless of grade and dose, are dermatological (palmar-plantar erythrodysesthesia syndrome [PPES], hyperkeratosis, keratosis pilaris, pruritus, alopecia, dry skin, erythema, melanocytic naevus, xerosis, rash), gastrointestinal (nausea, vomiting, decreased appetite), musculoskeletal (arthralgia, myalgia, pain in extremity), fatigue, asthenia, insomnia and headache. Overall, the most common AEs ($>20\%$) suspected to be related to encorafenib in all combination studies are nausea, diarrhea, vomiting, and fatigue. Other toxicities experienced in combination studies were: musculoskeletal (increased CPK, myalgia, arthralgia), gastrointestinal and eye-related toxicities in encorafenib combination with binimetinib. Dermatological events are reduced in the encorafenib combination with binimetinib. Clinically notable adverse events (by grouping) of encorafenib are primarily class effects of BRAF inhibitors, and are mostly characterized as identified risks: dermatological events, secondary neoplasms, gastrointestinal events, musculoskeletal disorder/pain, fatigue/asthenia, headache, facial paresis, and potential risk: liver events, ophthalmological events (retinal, vascular and other eye events), increased heart rate and acute renal failure.	
Maximum dose tested	Single Dose	700 mg QD
	Multiple Dose	700 mg QD, less than 15 days
Exposures Achieved at Maximum Tested Dose	Single Dose	700 mg QD C_{max}: 9030 ng/mL (13.4%) AUC_{inf}: 64,400 h*ng/mL (1.75%)
	Multiple Dose	550 mg QD (Day 15) C_{max}: 4490 ng/mL (49.1%) AUC_{tau}: 15,900 h*ng/mL (33.7%) (No data for 700 mg)
Range of linear PK	AUC and C_{max} of encorafenib are approximately dose proportional over the complete dose range studied (50 mg to 700 mg on Cycle 1 Day 1 and 50 mg to 550 mg on Cycle 1 Day 15).	
Accumulation at steady state	Accumulation ratio for AUC (Day 15/Day 1) was 0.48-0.54 across the 50 mg to 550 mg dose levels, indicating no dose-dependent change in accumulation	

Metabolites	In the human ADME study [CLGX818A2101], the predominant biotransformation reaction was N-dealkylation. Other major metabolic pathways involved hydroxylation, carbamate hydrolysis, indirect glucuronidation and glucose conjugate formation. A minor metabolic pathway involved desaturation. Various combinations of the above biotransformation reactions were also observed. The most abundant circulating component of the radioactivity in plasma was encorafenib (mean AUC of 27.5% following a single dose). The major circulating metabolites were M12.8 (an indirect glucuronide of encorafenib; 23.0%), M42.5A (derived from loss of the isopropyl-carbamic acid methyl ester; 15.5%), M17.3 (another indirect glucuronide of encorafenib; 6.2%) and M44 (derived from carbamate hydrolysis followed by deamination and reduction; 5.09%). The only direct phase I metabolite observed in this study that was at least 10% of total drug related exposure (AUC) was M42.5A, which was also found in both rat and monkey plasma. Preliminary results indicated that it is of lower potency compared to encorafenib and that it showed no significant safety signal in in vitro safety pharmacology testing	
Absorption	Absolute/Relative Bioavailability	Based on human ADME study, oral absorption is estimated to be at least 86%
	T _{max}	Across 50 – 550 mg dose levels following multiple doses, median encorafenib T _{max} tended to be 2 hours. The range across each individual dose level appears to be 0.5 – 4 hours.
Distribution	V _d /F or V _d	Human ADME mean (%CV) V _d /F = 235 L (31.4%)
	% bound	In vitro human plasma protein binding: 86.1% range of 84.4-86.8%
Elimination	Route	Human ADME: Metabolism is the major clearance pathway (>86% of radioactive dose) A mean of 47% of the radioactive dose was recovered in urine A mean of 39% of the radioactive dose was recovered in feces A mean of 1.8% of the dose was eliminated in the urine as unchanged encorafenib A mean of 5.0% of the dose was eliminated in the feces as unchanged encorafenib
	Terminal t _{1/2}	Human ADME mean (%CV) = 6.11 h (30%)
	CL/F or CL	Human ADME mean (%CV) CL/F = 27.9 L/h (32.8%)
Intrinsic Factors	Age	Intrinsic factors have not been evaluated. The sponsor will supplement the NDA submission with a population PK analysis that will evaluate these covariates as described in the Briefing Book in Table 2.
	Sex	
	Race	

	Hepatic & Renal Impairment	A hepatic impairment study is currently in conduct. Since preclinical and human ADME data indicate that encorafenib is primarily hepatically cleared, the sponsor plans to provide physiologically-based pharmacokinetic modeling (PBPK) and population pharmacokinetic (PK) analyses to predict exposure in patients with moderate or severe renal impairment in lieu of conducting a dedicated renal impairment study.
Extrinsic Factors	Drug interactions	A drug interaction study with a proton pump inhibitor and a study with a CYP3A4 inhibitor are currently in conduct. Data from both studies will be included in the NDA.
	Food Effects	A food effect study is currently in conduct
Expected High Clinical Exposure Scenario	Encorafenib has been studied at doses up to 700 mg, and has been shown to be dose proportional in the range of 50 – 700 mg following single dose and 50 mg to 550 mg following multiple doses. A 1.4-fold increase in C _{max} and a 1.6-fold increase in AUC _{tau} is observed at the 700 mg dose compared to the 450 mg following single dose. No increase in exposure is observed at the 550 mg dose compared to the 450 mg following multiple doses. Both patients (n = 2) receiving 700 mg encorafenib experienced dose limiting toxicities; one patient was discontinued from study treatment and the other patient was dose reduced to 450 mg.	

7.2 HIGHLIGHTS OF PRECLINICAL CARDIAC SAFETY

Nonclinical GLP cardiovascular safety pharmacology studies for encorafenib included an *in vitro* hERG evaluation and an *in vivo* telemetry study in the monkey.

The hERG IC₅₀ for encorafenib is 73.4 µM which supports a minimal clinical risk for QTc prolongation.

In the monkey telemetry study, single dose levels of 50, 100 or 200 mg/kg were evaluated. There were no changes at any dose level in systemic blood pressures (systolic, diastolic, mean arterial and pulse pressure), electrocardiographic intervals (PR, QT, QTc, QRS), body temperature or qualitative evaluation of ECG waveforms. At doses ≥ 50 mg/kg, higher heart rates were observed, with an apparent lack of diurnal shift in the heart rates as normally observed during the dark photo period. While TK data were not generated in the GLP CV telemetry study, exposures from the non-GLP dose-range finding monkey toxicology studies, where the same dose levels were evaluated, showed the following mean C_{max} and AUC (SD in parentheses) at the same dose levels:

	C _{max} (ng/mL)	AUC ₀₋₂₄ (h*ng/mL)
50 mg/kg	1,650 (1,550)	1,2800 (8,700)
100 mg/kg	5,580 (5,230)	4,3900 (24,900)
200 mg/kg	6,870 (1,400)	4,1400 (23,400)

7.3 HIGHLIGHTS OF CLINICAL CARDIAC SAFETY

As of the data-cutoff for the IB, a total of 4 healthy subjects and 341 patients with advanced cancer have received at least one dose of encorafenib as a single-agent in 5 studies:

- [CLGX818X2101] (n=107 enrolled): A Phase I multicenter, open-label, dose escalation study of oral encorafenib in adult patients with locally advanced or metastatic BRAF-mutant melanoma (dose escalation and expansion) or mCRC (dose expansion only). A total of 54 patients were treated in the dose escalation portion of the study at the following encorafenib doses (mg QD): 50 (n=4), 100 (n=10), 150 (n=6), 200 (n=4), 300 (n=5), 450 (n=6), 550 (n=5), and 700 (n=2). In addition, to the daily regimens, 3 twice daily dosing regimens (BID) were also evaluated (mg BID): 75 (n=3), 100 (n=5), 150 (n=4). A total of 53 patients were treated in the dose expansion portion of the study at the following doses: 450 mg QD (n=34), and 300 mg QD (n=17) and 300 mg QD increased to 450 mg QD at cycle, day 15 (n=2).
- [CLGX818AUS03] (n=12 enrolled): A Phase II, open label study to determine the efficacy and safety of treatment with encorafenib in patients with a diagnosis of select solid tumors or hematological malignancies that have been pre-identified to have BRAFV600 mutations and whose disease has progressed on or after standard treatment. All patients were treated with encorafenib 300 mg QD.
- [CLGX818X2102] (n=15, enrolled in single-agent encorafenib part): A phase II, multicenter, open-label study of sequential, single-agent encorafenib followed by a rational combination with targeted agents after progression, to overcome resistance in adult patients with locally advanced or metastatic BRAF V600 melanoma. All patients were treated in Part I of the study in which they received single agent encorafenib at a dose of 300 mg QD. One patient in the study received encorafenib 450 mg QD in combination with binimetinib 45 mg BID in Part II of the study.
- [CMEK162B2301] (n=207, enrolled in single-agent encorafenib arm): A 2-part phase III randomized, open label, multicenter study of encorafenib and binimetinib versus vemurafenib and encorafenib monotherapy in patients with unresectable or metastatic BRAF- V600- mutant melanoma. Patients randomized to the single-agent encorafenib arm were treated with 300 mg QD.
- [CLGX818A2101] (n=4 enrolled): A Phase I, single center, open-label study to investigate the absorption, distribution, metabolism and excretion (ADME) of encorafenib following a single oral dose of 100 mg [¹⁴C]encorafenib in healthy male subjects.

As of the data-cutoff in the IB, a total of 580 patients with advanced cancer have received at least one dose of encorafenib in combination with other targeted agents in the following 6 studies:

- [CMEK162X2110] (n=147 enrolled): A phase Ib/II, multicenter, open-label, dose escalation study of encorafenib in combination with binimetinib in adult patients with BRAF V600 - dependent advanced solid tumors. In the dose-escalation portion of the study, patients received encorafenib (mg QD)/binimetinib (mg BID) at the following dose levels: 50/45 (n=6), 100/45 (n=5), 200/45 (n=4), 400/45 (n=5), 450/45 (n=13), 600/45 (n=8), 800/45 (n=6). An additional 79 patients were enrolled in the dose expansion portion of the study at the following encorafenib (mg QD)/binimetinib (mg BID) doses: 600/45 (n=64), 450/45 (n=15).

- [CLGX818X2103] (n=132 enrolled): A phase Ib/II multi-center, open-label, dose escalation study of encorafenib and cetuximab or encorafenib, BYL719, and cetuximab in patients with BRAF- mutant metastatic colorectal cancer. A total of 54 patients were enrolled in the phase Ib portion of the study. Twenty-six patients enrolled in the dual combination arm received encorafenib (mg QD) and cetuximab 400 mg/m² followed by 250 mg/m² weekly: 100 (n=2), 200 (n=7), 400 (n=9), and 450 (n=8).

Twenty-eight patients enrolled in the triple combination arm received cetuximab 400 mg/m² followed by 250 mg/m² weekly in combination with encorafenib (mg QD)/BYL719 (mg QD): 200/100 (n=3), 200/200 (n=8), 200/300 (n=10), and 300/200 (n=7).

- [CLEE011X2105] (n=28 enrolled): A phase Ib/II, multicenter, study of LEE011 in combination with encorafenib in adult patients with BRAF-mutant melanoma. Patients received encorafenib (mg QD)/LEE011 (mg QD): 300/200 (n=6), 200/300 (n=12), 100/400 (n=6), and 200/400 (n=4).
- [CMEK162B2301] (n=231, enrolled in encorafenib+binimetinib combination arm): A 2-part phase III randomized, open label, multicenter study of encorafenib and binimetinib versus vemurafenib and encorafenib monotherapy in patients with unresectable or metastatic BRAF- V600- mutant melanoma. All the patients in the combination arm are treated with encorafenib 450 mg QD and binimetinib 45 mg BID.
- [CLGX818X2109] (n=38 enrolled): 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. Of the 37 patients treated, 36 received encorafenib 450 mg QD in combination with binimetinib 45 mg BID. One patient was inadvertently dosed with encorafenib 900 mg QD and binimetinib 45 mg BID.
- [CWNT974X2102C] (n=4): A phase Ib/II multi-center, open label, dose escalation study of WNT974, encorafenib and cetuximab in patients with BRAFV600- mutant KRAS wild-type metastatic colorectal cancer harboring Wnt pathway mutations. All 4 patients received encorafenib 200 mg QD in combination with WNT974X2102C 10 mg QD.

In the single-agent study of encorafenib [CLGX818X2101], an increase in QTcF from baseline of >30 msec was seen in 47 out of 105 evaluable patients (44.8%) in both the dose-escalation and dose-expansion phases; there were only 5 patients (4.8%) with an increase in QTcF > 60 msec. A new QTcF >480 msec was only observed in 2 patients (1.9%), and new QTcF >500 msec was not observed. No relationship between dose and notable ECGs was evident. Both patients with QTcF > 480 msec had abnormal ECG findings at Baseline with right bundle branch block and in one case, QTc prolongation was an isolated finding not confirmed on a subsequent ECG.

In the combination study of encorafenib and LEE011 [CLEE011X2105]: an increase in QTcF from Baseline of >30 msec was seen in 2 out of 14 evaluable patients (14.3%). There was no increase in QTcF from Baseline of > 60 msec. No cases of new QTcF >480 msec new QTcF >500 msec were observed.

In the combination study of encorafenib and binimetinib [CMEK162X2110]: an increase in QTcF from baseline of >30 msec was seen in 25 out of 64 evaluable patients 39.1%) in the phase Ib & II of binimetinib at 45 mg + encorafenib 600 mg (N=71). No patient had an increase in QTcF >60 msec. No cases of new QTcF >480 msec or new QTcF >500 msec were observed. An increase in QTcF from baseline of >30 msec was seen in 13 out of 31 evaluable patients 41.9%) in the phase Ib & II of binimetinib at 45mg + encorafenib at 400/450 mg (N=34). No patients had an increase in QTcF >60 msec. A new QTcF >480 msec was observed in 1 patient (3.2%), and no case of new QTcF >500 msec was observed.

The case of QTcF >480 msec occurred in a 64-year-old male patient with metastatic lung adenocarcinoma (brain and bone). The medical history included gout, hypertension and hyperlipidemia. Prior medications were allopurinol, simvastatin, losartan, denosumab and zoledronic acid (for bone metastasis) and chemotherapy agents gemcitabine, carboplatin and pemetrexed. Baseline ECG was within normal limits. Patient started study medications encorafenib 450 mg QD and binimetinib 45mg BID without any incidence. At cycle 9 day 1 pre-dose, patient presented QTc interval of 525 msec (grade 3 absolute QTc value) and QTcF of 499 msec (grade 2 absolute QTcF value). The electrolytes of sodium, potassium, magnesium and calcium were within normal limits. Study drugs had been interrupted only once at cycle 4 due to a Grade 1 AE of headache. The event of grade 3 absolute QTc value was not reported as an AE/SAE by the investigator.

Cardiac AEs

The encorafenib safety database was searched for events of torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation, ventricular flutter, syncope and seizures using the MedDRA version 18.1 Standardized MedDRA Queries (SMQs) Torsade de pointes/QT prolongation (broad), Ventricular tachyarrhythmias (narrow) and Convulsions (narrow).

Three cases were identified in patients treated with encorafenib as a single agent. One of the cases was classified as status epilepticus and the other 2 were classified as seizures. All three patients had central nervous metastases.

A total of 20 cases were identified in patients who received encorafenib in combination with binimetinib. Seizure or partial seizure, or epilepsy was noted in 13 patients, 8 of whom had central nervous system metastases. Concomitant serious adverse events included gastric ulcer haemorrhage, multi-organ failure, and pneumonia in one patient, urosepsis in one patient, pneumonia, hemiparesis, and anaemia in the 3rd patient, and microangiopathic encephalopathy in the last patient. In addition to the patients with seizures, there were 4 patients experienced syncope. The syncope was diagnosed with vasovagal syncope in one patient and another patient had a history of vestibular neuronitis. In the 3rd patient, associated serious adverse events included gastrointestinal haemorrhage and anaemia. There were a total of 3 patients with cardiovascular events documented as cardio-respiratory arrest (n=2), and cardiac arrest (n=1). One of the patients with cardio-respiratory arrest had an associated event of pericarditis and the patient with cardiac arrest had an associated event of pericarditis.

A total of 6 cases were identified in patients who received encorafenib in combination with agents other than binimetinib. Two patients who received encorafenib in combination with the

CDK 4/6 inhibitor, LEE011 experienced seizures and both had central nervous system metastases. The other 4 patients experienced encorafenib in combination with cetuximab. Among the 2 patients with cardiac arrest, 1 patient experienced ventricular fibrillation, myocardial infarction and pneumonia. Following a coronary artery stent placement, the patient had cardiac arrest. Syncope was observed in 1 patient and was associated with hypotension at the time of the event. Finally, one patient was found to have electrocardiogram QT prolongation. Concomitant findings included possible inferior wall infarction and increased cardiac enzymes.

There were 2 cases in patients who received encorafenib in combination with binimetinib and a 3rd agent. One patient received binimetinib, encorafenib, and the PI3K inhibitor BKM120 with central nervous system metastases experienced seizure and a 2nd patient who received binimetinib, encorafenib, and LEE011 experienced syncope which was attributed to laterocervical lymph node disease.

In summary, nearly all the cardiovascular, and central nervous system events which were searched in the encorafenib safety database were observed in patients treated with encorafenib in combination with other agents and in patients with co- morbidities which could have contributed to the events described.

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/s/

DHANANJAY D MARATHE

12/11/2017

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