

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210498Orig1s000

OTHER REVIEW(S)

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

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

Date: June 1, 2018

To: Anuja Patel, MPH
Senior Regulatory Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products (OHOP)

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

Subject: OPDP Labeling Comments for MEKTOVI (binimetinib) tablets, for oral use

NDA: 210498

In response to DOP1 consult request dated August 15, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI) and carton and container labeling for the original NDA submission for MEKTOVI (binimetinib) (Mektovi).

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 13, 2018, and we have no comments. OPDP's comments on the proposed draft PI and 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
06/01/2018

**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: Patient Package Insert (PPI)

Drug Name (established name): MEKTOVI (binimetinib)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 210498

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) 210498 for MEKTOVI (binimetinib) tablets. The proposed indication for MEKTOVI (binimetinib) tablets is in combination with encorafenib, 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 28, 2017 and August 15, 2017, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for MEKTOVI (binimetinib) tablets.

2 MATERIAL REVIEWED

- Draft MEKTOVI (binimetinib) tablets PPI received on June 30, 2017, and received by DMPP and OPDP on May 23, 2018.
- Draft MEKTOVI (binimetinib) tablets Prescribing Information (PI) received on June 30, 2017 and revised on August 16, 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 PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI 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

**CDRH Consult
MEMORANDUM**

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



NDA210498/ICC1600862/S002

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:

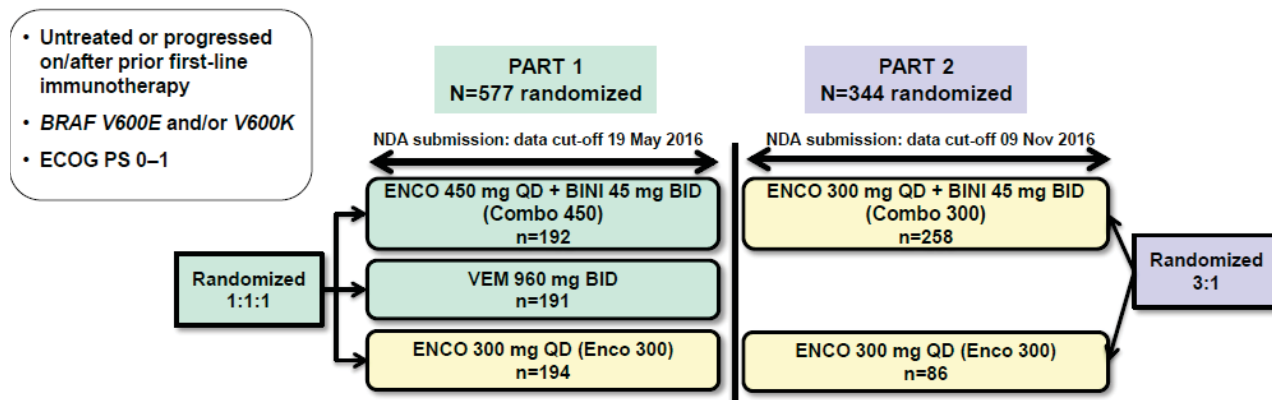
Approximately 576 Patients will be randomized 1:1:1 to one of 3 treatment arms:

- 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). 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 (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 (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 with 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

2018.04.02

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/s/

CARYL J GIULIANO
04/02/2018

LABEL AND LABELING REVIEW

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)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 5, 2018
Requesting Office or Division:	Division of Oncology Products (DOP2)
Application Type and Number:	NDA 210498
Product Name and Strength:	Mektovi (binimetinib) Tablets, 15 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Array Biopharma Inc.
FDA Received Date:	June 30, 2017 and August 16, 2017
OSE RCM #:	2017-1310
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

This review responds to a DOP2 consult request for DMEPA to evaluate the proposed Mektovi container labels, carton labeling, and Prescribing Information (PI) for areas of vulnerability that can lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of materials found redundancy of the dosage form statement which contributes to clutter on the container label and carton labeling. Thus, we have provided a recommendation in Section 4.1.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI is acceptable from a medication error perspective. However, the proposed container labels and carton labeling for Mektovi (binimetinib) Tablets can be improved to eliminate clutter and reduce redundancy on the principal display panel.

4.1 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 dosage form statement, “tablets”, appears three times on the principal display panel. To eliminate clutter and reduce redundancy of information, remove the word “Tablets” in the strength statement, “15 mg Tablets”.

APPEARS THIS WAY ON ORIGINAL

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Mektovi received on August 16, 2017 from Array BioPharma Inc.

Table 2. Relevant Product Information for Mektovi	
Initial Approval Date	N/A
Active Ingredient	binimetinib
Indication	indicated in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test.
Route of Administration	Oral
Dosage Form	Tablets
Strength	15 mg
Dose and Frequency	45 mg (three 15 mg tablets) orally every 12 hours. Maximum daily dose is 90 mg. For patients with moderate or severe hepatic impairment, the recommended dose is 30 mg orally twice daily.
How Supplied	15 mg: Supplied in cartons; each containing a bottle of 180 tablets
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].
Container Closure	(b) (4)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Mektovi labels and labeling submitted by Array BioPharma Inc.

- Container label; submitted June 30, 2017
- Carton labeling; submitted June 30, 2017
- Prescribing Information; submitted August 16, 2017 (image not shown)

G.2 Label and Labeling Images

Container Label: 15 mg; 180 count (submitted June 30, 2017)



^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Container Label: 15 mg; 180 count (submitted June 30, 2017)

(b) (4)



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

/s/

JANINE A STEWART
03/05/2018

CHI-MING TU
03/05/2018

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	(b) (4)
Brand Name	MEKTOVI
Generic Name	Binimetinib (MEK162)
Sponsor	Array BioPharma Inc.
Indication	(b) (4)
Dosage Form	15 mg tablets
Drug Class	Inhibitor of mitogen-activated protein kinase (MEK) 1 and MEK 2
Therapeutic Dosing Regimen	45 mg orally twice daily
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	45 mg BID
Submission Number and Date	001 6/30/2016
Review Division	DOP2

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

In the pooled analysis across 7 clinical studies in subjects receiving MEKTOVI, a relatively flat relationship between $\Delta QTcF$ and concentrations of binimetinib or metabolite AA00426032 was observed. Based on the observed concentration- $\Delta QTcF$ relationship, no large QTc prolongation (20 ms) is estimated following 45 BID.

We focused on the data from ARRAY-162-111 study and CMEK162A2301 for central tendency sensitivity analysis because ARRAY-162-111 included the suprathreshold dose of 60 mg BID and CMEK162A2301 is the large pivotal trial and both of them had replicate ECG measurement around T_{max} at the steady state. For E14 central tendency analysis, no large QTc prolongation at 45 mg BID and 60 mg BID were observed (the largest upper bounds of the 2-sides 90% CIs for the mean $\Delta QTcF < 20$ ms) (Table 1). The study did not include positive control (moxifloxacin) arm, therefore no assay sensitivity was established.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Binimetinib (Dose-Pooled at 45 mg BID and 60 mg BID) (ARRAY-162-111 and CMEK162A2301, FDA Analysis)

Study	BID Doses (mg)	Total N	Visit	Time	Mean	Std Dev	90% CI for Mean
ARRAY-162-111	45	44	CYCLE 2 DAY 1	1.5	4.7	18.6	(-1.1, 10.5)
	60	34	CYCLE 2 DAY 1	0	4.8	23.2	(-2.0, 11.5)
CMEK162A2301	45	230	Week 1 Day 1	1.5	0.2	16.4	(-1.6, 2.0)
	45	296	> Week 1 Day	1.5	0.1	20.3	(-1.9, 2.0)

The supratherapeutic dose (60 mg BID) produces mean C_{max} values 1.21-fold the mean C_{max} of therapeutic dose 45 mg BID at day 15 (steady state). The impacts of age, race, gender, body weight, hepatic and renal impairment, effect of genotype and drug-drug interactions are being evaluated. Based on the C-QTc relationship, clinically relevant large QTc prolongation is not expected in subjects with intrinsic/extrinsic factors that increase drug exposure.

2 PROPOSED LABEL

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

3 BACKGROUND

3.1 PRODUCT INFORMATION

Binimetinib is a potent and selective allosteric, adenosine triphosphate (ATP)-uncompetitive inhibitor of mitogen-activated protein kinase (MEK) 1 and MEK 2. It is active in inhibiting pERK and growth of BRAF mutant cancer cells in the low nano-molar range.

3.2 MARKET APPROVAL STATUS

Binimetinib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

See Appendix 6.1

3.4 PREVIOUS CLINICAL EXPERIENCE

See Appendix 6.1

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of binimetinib's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT has agreed to the sponsor's proposal under (b) (4) that QT/QTc assessment from the proposed clinical studies is likely to be sufficient to rule out large QT prolongation (i.e., >20 ms) for binimetinib at the therapeutic dose. The sponsor submitted the cardiac safety report CP-16-002 for the binimetinib and its metabolite AA00426032, including electronic datasets pooled from 7 clinical trials and waveforms to the ECG warehouse.

4.2 QT STUDY

4.2.1 Title

The cardiac safety analysis of binimetinib: STUDY Nos. ARRY-162-0601, ARRY-162-0602, ARRAY-162-111, CMEK162X1101, CMEK162A2101J, CMEK162X2201, and CMEK162A2301.

4.2.2 Protocol Number

- ARRY-162-0601: Phase I, Randomized, Placebo-Controlled, Double-Blind Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Ascending Doses of ARRY-438162 in Healthy Volunteers
- ARRY-162-0602: Phase I, Randomized, Placebo-Controlled, Double-Blind Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of ARRY-438162 in Healthy Volunteers
- ARRAY-162-111: A Phase 1 Dose-escalation Study of Oral ARRY-438162 in Patients with Advanced Solid Tumors Followed by Expansion Cohorts in Patients with Advanced

or Metastatic Biliary Cancer or Metastatic Colorectal Cancer

- CMEK162A2101J: A Randomized, Single-Center, Open-Label, Two-Sequence, Two-Period Cross-Over Study to Investigate the Relative Bioavailability of MEK162 Novartis CSF and Array CSF Following a Single Oral Dose Given as 3 x 15 mg Tablets in Healthy Subjects
- CMEK162X1101: A Phase I study of Oral MEK162 in Japanese Patients with Advanced Solid Tumors
- CMEK162X2201: A Phase II, Open-Label Study to Assess the Safety and Efficacy of Oral MEK162 in Adults with Locally Advanced and Unresectable or Metastatic Malignant Cutaneous Melanoma, Harboring BRAFV600 or NRAS Mutations
- CMEK162A2301: The NEMO trial (NRAS melanoma and MEK inhibitor): A Randomized Phase III, Open Label, Multicenter, Two-Arm Study Comparing the Efficacy of MEK162 versus Dacarbazine in Patients with Advanced Unresectable or Metastatic NRAS Mutation-Positive Melanoma

4.2.3 Study Dates

Date of last completed (Data cut-off date for ongoing studies):

- ARRY-162-0601: 25 June 2006
- ARRY-162-0602: 08 May 2007
- ARRAY-162-111: 25 January 2013
- CMEK162A2101J: 01 Apr 2013
- CMEK162X1101: Ongoing (Not applicable)
- CMEK162X2201: Ongoing (07-Jan-2014)
- CMEK162A2301: Ongoing (24-Aug-2015)

4.2.4 Objectives

The primary objective of this analysis was to evaluate the potential of binimetinib and AR00426032 to delay cardiac repolarization as measured by QTc prolongation.

Secondary objectives were to characterize the effect of binimetinib and AR00426032 on heart rate (HR).

4.2.5 Study Description

4.2.5.1 Design

A summary of study characteristics is provided in the following table.

Table 3-1. Summary of the Studies Included in the Analysis

Study Number (population)	No. of Subjects	Dose Regimen, Dose and Sample Size	ECG Methods and Frequency	PK Assessment ^a
ARRY-162-0601 (healthy volunteers)	N=20 ^b	Single Doses • 5 mg, N=4 • 10 mg, N=4 • 20 mg, N=4 • 30 mg, N=4 • 40 mg, N=4	12-lead ECG triplicate, 5 min apart: • Screening • 2 h post-dose • 24 h post dose • Discontinuation/Termination	• 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 36, and 48 hours post-dose
ARRY-162-0602 (healthy volunteers)	N=38 ^b	QD doses • 5 mg, N=6 • 10 mg, N=6 • 20 mg, N=4 • 40 mg, N=6 • 60 mg, N=6 BID doses • 20 mg, N=6 Single dose • 80 mg, N=4	12-lead ECG triplicate, 5 min apart: • Screening • 2 h post-dose Day 1 • 2 h post-dose Day 8 • 2 h post-dose Day 14 • Discontinuation/Termination	• 0.5, 1, 1.5, 2, 3, 4, 8, 12 and 24 hours post-dose on Day 1 • Pre-dose on Day 8 • 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 48 hours post-dose on Day 14
CMEK162A2101J (healthy volunteers)	N=37	Single Dose • 45 mg, N=37	12-lead ECG triplicate, 5 min apart: • Baseline • Pre-dose and 1, 3, 5 and 24 hours post-dose per period (Days 1 and 9) • End of treatment	• Days 1 and 9: 0, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48 and 72 hours post-dose
ARRAY-162-111 (cancer patients)	N=93	BID doses • 30 mg, N=4 • 45 mg, N=44 • 60 mg, N=41 • 80 mg, N=4	12-lead ECG triplicate, 5-10 min apart: • Screening • Pre-dose and between 1-2 h post-dose: Cycle 1 Days 1, 8, and 15; Day 1 of subsequent cycles • Discontinuation visit	• Cycle 1: pre-dose on Day 1, Day 8, and Day 15. • Pre-dose of Day 1 of subsequent cycles • Cycle 1 Day 15 and Cycle 3 Day 1: 0.5, 1.5, 4 and 8 h post-dose
CMEK162X1101 (Japanese cancer patients with KRAS, NRAS or BRAFV600 mutations)	N=21	BID doses • 30 mg, N=6 • 45 mg, N=15	12-lead ECG, triplicate, 5-10 min apart: Pre-dose of Cycle 1 Day 1 12-lead ECG, duplicate, 5-10 min apart: • Screening • Predose on Cycle 1 Days 8, 15, and 22; Cycle 2 Days 1 and 15 and Day 1 of subsequent cycles • End of Treatment	• Cycle 1 Day 1: 0, 0.5, 1.5, 2, 3, 4, 8, and 12 h • Pre-dose on Cycle 1 Days 2 and 8 • Cycle 1 Day 15: 0, 0.5, 1.5, 2, 3, 4, 8, and 12 h • Pre-dose on Cycle 1 Day 16 • Pre-dose on Day 1 of cycles 2 and 3
CMEK162X2201 (melanoma patients with NRAS or BRAFV600 mutations)	N=183	BID doses • 45 mg, N=158 • 60 mg, N=25	12-lead ECG, triplicate, 5 min apart: • Screening • Pre-dose of Day 1 of every cycle. • End of treatment	• Cycle 1 Day 1: pre-dose • Cycle 1 Day 15: pre-dose and 3 h post-dose • Pre-dose on Day 1 of Cycle 3 and subsequent cycles

CMEK162A2301 NEMO (NRAS positive melanoma)	N = 269 ^b	• 45 mg BID, N=269	12-Lead ECG, triplicate: Screening 12-Lead ECG, non-triplicate: • Days 1, 22, and 43: 1.5 h post-dose • Pre-dose on Days 22 and 43 and approximately every 3 weeks thereafter • End of treatment	• Day 1: between 0.2 – 1 h post-dose, 1.5 h post-dose, between 4-10 h post-dose • Days 22 and 43: 1.5 h post-dose
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^a Limited/sparse sampling schemes listed for ARRAY-162-111 and CMEK162X2201. ^b Binimetinib arms
 No.: number; ECG: electrocardiogram; PK: pharmacokinetic; BID: twice-daily; N: Number of subjects

Reviewer's comments: The pooled studies are acceptable. They included therapeutic and supratherapeutic doses. ECG quality and measuring time are acceptable.

4.2.5.2 Controls

No placebo and positive control for ECG. Without adequate control, the studies are not adequate to exclude the effect of small QTc prolongation (10 ms).

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

ECG and PK data were pooled from 7 clinical trials in healthy and cancer patients. Healthy subjects were treated with doses ranging from 5 to 80 mg total daily dose. Patients with advanced cancer have received binimetinib at doses of 30 to 80 mg BID.

4.2.6.2 Sponsor's Justification for Doses

Not provided for QT assessment.

Reviewer's Comment: The 45 mg BID selected for the pivotal phase III study is the proposed therapeutic dose. The supratherapeutic dose (60 mg BID which is also the MTD) produces mean C_{max} values 1.21-fold and 0.77-fold the mean C_{max} with therapeutic dose 45 mg BID for the parent drug and metabolite at day 15 (steady state) respectively.

4.2.6.3 Instructions with Regard to Meals

Binimetinib can be taken with or without food.

Reviewer's Comment: The effect of food on the peak plasma concentrations of binimetinib is mild. Compared to fasted conditions, the low-fat meal increased the estimated geometric mean C_{max} of binimetinib by about 29% on average while the high-fat meal decreased it by about 17% on average.

4.2.6.4 ECG and PK Assessments

See the table in section 4.2.5.1.

Reviewer's Comment: Overall, the timing of the ECGs and PK collection is acceptable to capture the drug effect around T_{max} after first dose and at steady state.

4.2.6.5 Baseline

Baseline ECG measurements were calculated as described in each study protocol:

- ARRAY-162-111: Average of triplicate ECG measurements at screening and pre-dose on Cycle 1 Day 1
- CMEK162X1101: Average of triplicate ECG measurements at pre-dose on Cycle 1 Day 1
- CMEK162X2201: Average of the triplicate ECG measurements at screening
- ARRAY-162-0601 and ARRAY-162-0602: Average of triplicate ECG measurements at screening
- CMEK162A2101J: Average of triplicate pre-dose ECG measurements on each respective day with PK sampling (Days 1 and 9)
- CMEK162A2301: Average of triplicate ECG measurements at screening

4.2.7 ECG Collection

Standard 12-Lead ECGs were obtained according to the respective protocols.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

There were a total of 666 ECG evaluable subjects across the seven studies (ARRAY-162-0601, ARRAY-162-0602, ARRAY-162-111, CMEK162X1101, CMEK162A2101J, CMEK162X2201, and CMEK162A2301).

Table 4-1. Data Summary for the Concentration-QTc Analyses

Study	Binimetinib Concentration-ΔQTcF			
	All Conc-ΔQTcF Pairs		Valid Conc-ΔQTcF Pairs	
	N _{obs}	N _{subj}	N _{obs} (% of all pairs)	N _{subj} (% of all pairs)
ARRAY-162-111	425	87	292 (68.7%)	82 (94.3%)
ARRAY-162-0601	40	20	38 (95%)	20 (100%)
ARRAY-162-0602	76	38	76 (100%)	38 (100%)
CMEK162A2301	1118	256	708 (63.3%)	231 (90.2%)
CMEK162X1101	71	21	52 (73.2%)	21 (100%)
CMEK162X2201	259	97	112 (43.2%)	53 (54.6%)
MEK162A2101J	317	37	317 (100%)	37 (100%)
Total	2306	556	1595 (69.2%)	482 (86.7%)
Study	AR00426032 Concentration-ΔQTcF			
	All Conc-ΔQTcF Pairs		Valid Conc-ΔQTcF Pairs	
	N _{obs}	N _{subj}	N _{obs} (% of all pairs)	N _{subj} (% of all pairs)
ARRAY-162-111	425	87	292 (68.7%)	82 (94.3%)
ARRAY-162-0601	40	20	38 (95%)	20 (100%)
ARRAY-162-0602	76	38	76 (100%)	38 (100%)
CMEK162A2301	1118	256	708 (63.3%)	231 (90.2%)
CMEK162X1101	71	21	52 (73.2%)	21 (100%)
CMEK162X2201	259	97	112 (43.2%)	53 (54.6%)
MEK162A2101J	316	37	316 (100%)	37 (100%)
Total	2305	556	1594 (69.2%)	482 (86.7%)

ΔQTcF: change from baseline in rate-corrected QT interval using Fridericia's method; Conc: concentration; N_{obs}: number of observations; N_{subj}: number of subjects

4.2.8.2 Statistical Analyses

4.2.8.2.1 Central Tendency Analysis

The sponsor did not report the central tendency by-time analysis.

Reviewer's Comments: We provided our independent analysis in Section 5.2.

4.2.8.2.2 Assay Sensitivity

No assay sensitivity established.

4.2.8.2.3 Categorical Analysis

Two subjects absolute QTcF values >500 ms and two subjects' changes from baseline ≥ 60 ms were observed.

Source: Clinical study report for Array-162-111, page 74/132

4.2.8.3 Safety Analysis

The binimetinib global 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 19.0 Standardized MedDRA Queries (SMQs) Torsade de pointes/QT prolongation (broad), Ventricular tachyarrhythmia (narrow) and Convulsions (narrow). There were a total of 45 cases captured with this search. There were no reported events of torsade de pointes, ventricular tachycardia, ventricular fibrillation or ventricular flutter.

The majority of the cases (n=35) were due to reported events of seizure (n=25) and syncope (n=10). Of the cases of seizure, the largest number of cases (n=19) were associated with documented brain metastases associated with progression of disease. In addition, there were 2 cases assessed as related to progression of disease, 1 due to Posterior Reversible Encephalopathy Syndrome (PRES), 1 due to microangiopathic encephalopathy and 1 due to sepsis. In addition, there was one patient who experienced a seizure in the setting of gastrointestinal hemorrhage and multi-organ failure while receiving binimetinib in combination with encorafenib. This patient did expire due to the multi-organ failure. The investigator assessed this event as not related to the study drugs.

Of the cases of syncope, 6 had clearly identified explanations or alternative causes (dehydration with hypotension, anemia with hypotension, vestibular neuronitis, excessive exercise with dehydration, progression of disease with cervical lymphadenopathy which the investigator associated with the syncope episode and gastrointestinal bleeding). Furthermore, 2 of these cases had specific mention of no ECG findings and a negative cardiac evaluation.

There was one syncopal event in a patient receiving binimetinib and encorafenib which was diagnosed as "vasovagal" but the investigator could not rule out that it was due to study drugs. There was a cardiology consultation with an assessment that the event was not cardiogenic. The investigator had noted a possibility of disease progression as an alternative cause.

There was one syncopal event in a patient participating in a hepatic impairment study and receiving binimetinib. Although a cardiogenic origin for the event was considered, there was also an observation that the patient was alcohol intoxicated.

There were two syncopal events for which there was limited information, no clear alternative causality, but the investigator assessed both cases as not related to study drug(s). One case in a patient who received single-agent binimetinib was evaluated and found to have no cardiac abnormalities. The other case occurred in a patient receiving binimetinib in combination with encorafenib with reported recurrent fainting episodes, but very limited information.

There were 8 cases of cardio-pulmonary arrest captured in this search. Of these, 6 were reported with clear alternative causality of progression of disease, fentanyl overdose and heart failure. There was one case of cardio-respiratory arrest in a patient receiving binimetinib in combination with encorafenib and for which there was an important finding of pericarditis. The investigator had assessed this event of cardio-respiratory arrest as related to study drugs. There was one additional case of sudden death in a patient receiving binimetinib in combination with FOLFOX and for which there was very limited information. The investigator assessed this event as not related to study drugs, but likely related to an acute cardiac event or a pulmonary embolism.

Finally, there were 2 cases of QT prolongation reported from this search. One case involved a patient receiving binimetinib as a single agent and who was found to have QT prolongation on an ECG examination associated with a Grade 2 increase in CK, but was otherwise asymptomatic. This patient was also found to have a mild increase in Troponin T and NT-proBNP. The binimetinib treatment was interrupted and the events resolved. The investigator assessed the events as related to binimetinib.

The other case involved a patient receiving binimetinib in combination with erlotinib. On Day 15 of Cycle 1, a scheduled ECG found a Grade 3 QTc of 516msec with repeat finding of 523msec. The event was assessed as a dose limiting toxicity in this study and related to binimetinib. There were no reported symptoms or other findings. Binimetinib was discontinued and one week later a repeat ECG reported an improvement to Grade 1 QTc prolongation. It was also noted at this time that the patient had progressive disease with brain metastases. The outcome of the QTc prolongation was not reported. It is not clear whether or not the progression of disease had an impact on the findings of QTc prolongation.

In a summary analysis of these reports from the global safety database search, aside from the observation of two events of prolonged QTc which were not associated with symptoms or complications and for which a relationship to binimetinib is not clear, there were no other events of high grade arrhythmias, seizures, syncope or cardiac arrest/sudden death which suggest an association with QT prolongation. There are clear alternative explanations for the vast majority of these events, as well as the potential of comorbidities and concomitant medications that may explain the finding.

Reviewer's comment: Safety data do not suggest binimetinib caused cardiac AEs associated with delayed cardiac repolarization.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented for the parent drug in Table 2 and Figure 1 and for the metabolite in Table 3 and Figure 2. In general, the exposure of binimetinib and its metabolite AR00426032

appeared to increase in a dose-proportional manner following administration of binimetinib over all single and multiple dose levels (5-80 mg QD), regardless of formulation. The mean therapeutic C_{max} from the Phase 2 study in patients with advanced and unresectable or metastatic cutaneous melanoma harboring a BRAF V600E or NRAS mutation (CMEK162X2201) at 45 mg dose is 439 ng/mL.

Table 2: Pharmacokinetics of Binimetinib Following Multiple Doses

Study Code/ Dose and Regimen (n)	Pharmacokinetic Parameter on Day 14 or 15 ¹							
	C _{max} ² ng/mL	T _{max} ³ hr	AUC ₀₋₈ ² ng/mL*hr	AUC ₀₋₁₂ ² ng/mL*hr	RAUC ^{2,4}	LF ^{2,4}	CL/F ² L/hr	V _z /F ² (L)
ARRAY-162-0602								
5 mg QD (6)	34.5 (11.5)	0.750 (0.483 - 1.48)	117 (18.4)	139 (19.8)	0.926 (10.4)	0.893 (13.3)	30.1 (20.0)	227 (32.9)
10 mg QD (6)	82.9 (21.3)	0.750 (0.500 - 1.48)	228 (18.9)	269 (17.5)	1.24 (11.2)	1.15 (9.69)	30.9 (13.8)	270 (45.2)
20mg QD (4)	144 (40.9)	1.24 (0.500 - 1.50)	440 (22.8)	520 (21.0)	1.06 (8.67)	0.991 (7.64)	31.2 (22.3)	349 (20.5)
40 mg QD (6)	415 (40.8)	1.50 (0.500 - 2.00)	1390 (30.7)	1600 (29.8)	1.32 (35.6)	1.23 (35.5)	20.7 (28.1)	303 (NC)
60 mg QD (6)	446 (22.1)	1.25 (1.00 - 2.00)	1680 (29.7)	1980 (31.4)	1.33 (34.7)	1.23 (28.5)	25.0 (32.5)	230 (NC)
20 mg BID (6)	251 (33.6)	1.53 (1.50 - 3.98)	1070 (31.2)	1270 (31.1)	2.05 (19.8)	NA (NA)	15.7 (31.1)	155 (44.0)
ARRAY-162-111								
30mg BID (4)	417 (39.9)	1.50 (1.50 - 3.83)	NC	ND	NC	NC	NC	NC
45 mg BID (4)	273 (64.7)	2.00 (1.07 - 2.87)	1490 (NC)	ND	1.50 (NC)	NC	NC	NC
60mg BID (7)	512 (30.8)	3.00 (0.53 - 7.12)	1820 (14.4)	ND	1.17 (18.4)	NC	NC	NC
60mg BID (7) (Expansion Phase)	594 (68.8)	1.50 (1.00 - 7.02)	3760 (NC)	ND	2.50 (NC)	NC	NC	NC
CMEK162X1101								
30mg BID (5)	400 (41.9)	2.02 (0.5 - 8)	ND	2430 (38.3)	1.44 (10.7)	ND	8.20 (NC)	58 (NC)
45 mg BID (9)	771 (31.0)	1.5 (0.5 - 2)	ND	3550 (27.7)	1.72 (33.6)	ND	14.8 (10.2)	69.7 (27.8)
CMEK162X2201								
45 mg BID (22)	438.5 (53.9)	1.48 (0.42 - 8.00)	ND	2103 (38.4)	1.31 (NC)	ND	20.2 (24.1)	NC
60mg BID (20)	531.3 (49.0)	1.42 (0.00 - 5.17)	ND	2637 (20.8)	1.40 (10.3)	ND	21.2 (24.9)	NC

¹ ARRAY-162-0602 = Day 14, ARRAY-162-111, CMEK162X1101 and CMEK162X2201 = Day 15

² Geometric mean (5CV)

³ Median (min-max)

⁴ ARRAY-162-111 = AUC₀₋₈, CMEK162X1101 and CMEK162X2201 = AUC₀₋₁₂

Source: Clinical Pharmacology Report (b) (4) Page 23

Table 3: Pharmacokinetics of AR00426032 Following Multiple Doses

Study Code/ Dose and Regimen (n)	Pharmacokinetic Parameter on Day 14 or 15 ¹				
	C _{max} ² ng/mL	T _{max} ³ hr	AUC ₀₋₈ ² ng/mL*hr	AUC ₀₋₁₂ ² ng/mL*hr	R _{AUC} ^{2,4}
ARRAY-162-0602					
5 mg QD (6)	NC	NC	NC	NC	NC
10 mg QD (6)	6.54 (19.1)	1.00 (0.500 - 1.48)	NC	NC	NC
20mg QD (4)	14.2 (4.58)	1.48 (0.983 - 1.50)	NC	NC	NC
40 mg QD (6)	15.3 (39.2)	1.25 (0.983 - 1.98)	NC	NC	NC
60 mg QD (6)	18.3 (68.0)	1.75 (1.00 - 2.00)	112 (NC)	NC	NC
20 mg BID (6)	12.9 (28.7)	1.77 (1.50 - 3.98)	78.9 (NC)	108 (NC)	1.04 (NC)
ARRAY-162-111					
30mg BID (4)	26.2 (47.6)	2.58 (1.50 - 3.83)	NC	ND	NC
45 mg BID (4)	46.2 (77.8)	2.00 (1.07 - 7.08)	287 (NC)	ND	1.40 (NC)
60mg BID (7)	27.8 (101)	2.00 (1.00 - 7.12)	137 (60.4)	ND	0.869 (31.3)
60mg BID (7) (Expansion Phase)	15.2 (111)	2.00 (0 - 3.00)	349 (NC)	ND	1.05 (NC)
CMEK162X1101					
30mg BID (5)	13.4 (118)	3 (1.5 - 8)	ND	236 (88.6)	NC
45 mg BID (9)	43.6 (84.0)	1.75 (1.5 - 2)	ND	286 (59.3)	NC
CMEK162X2201					
45 mg BID (22)	33.0 (73.6)	1.50 (0.50-7.98)	ND	254 (NC)	NC
60mg BID (20)	25.5 (124)	1.50 (0.00 - 8.00)	ND	322 (NC)	1.02 (NC)

¹ ARRAY-162-0602 = Day 14, ARRAY-162-111, CMEK162X1101 and CMEK162X2201 = Day 15

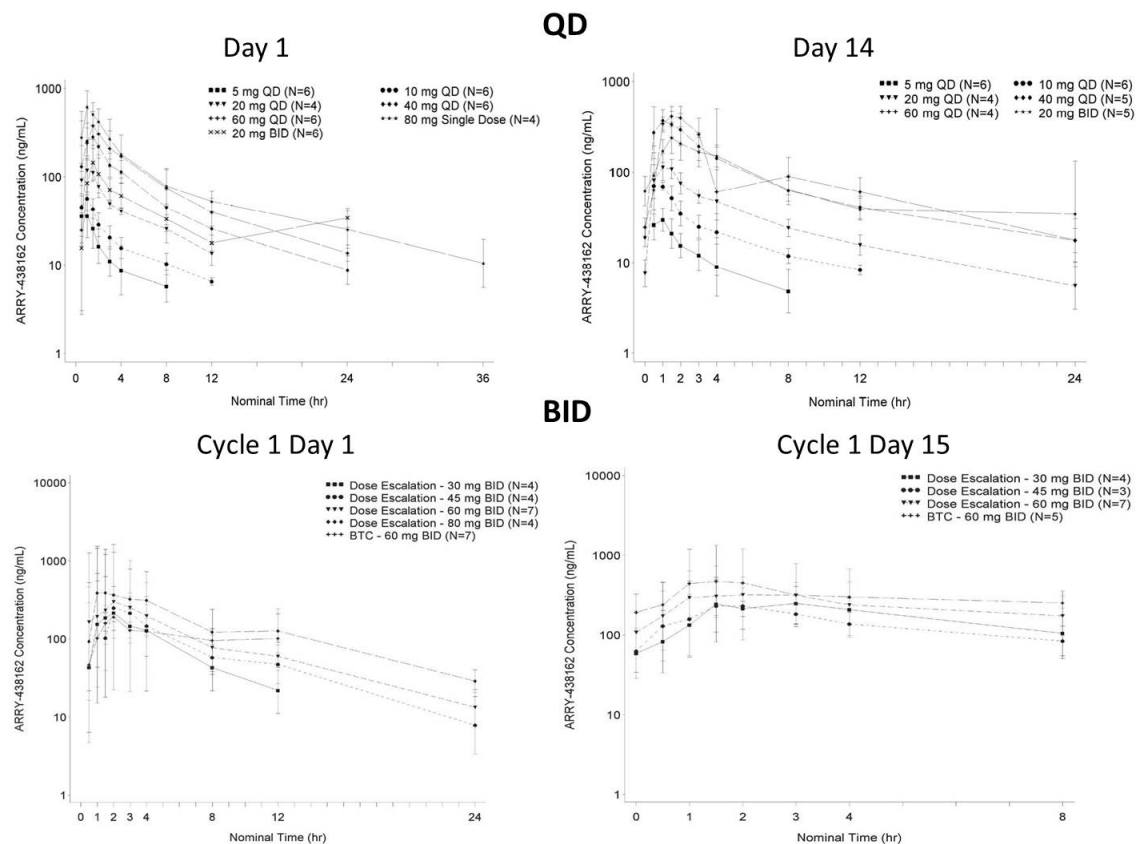
² Geometric mean (%CV)

³ Median (min-max)

⁴ ARRAY-162-111 = AUC₀₋₈, CMEK162X1101 and CMEK162X2201 = AUC₀₋₁₂

Source: Clinical Pharmacology Report (b) (4) Page 24

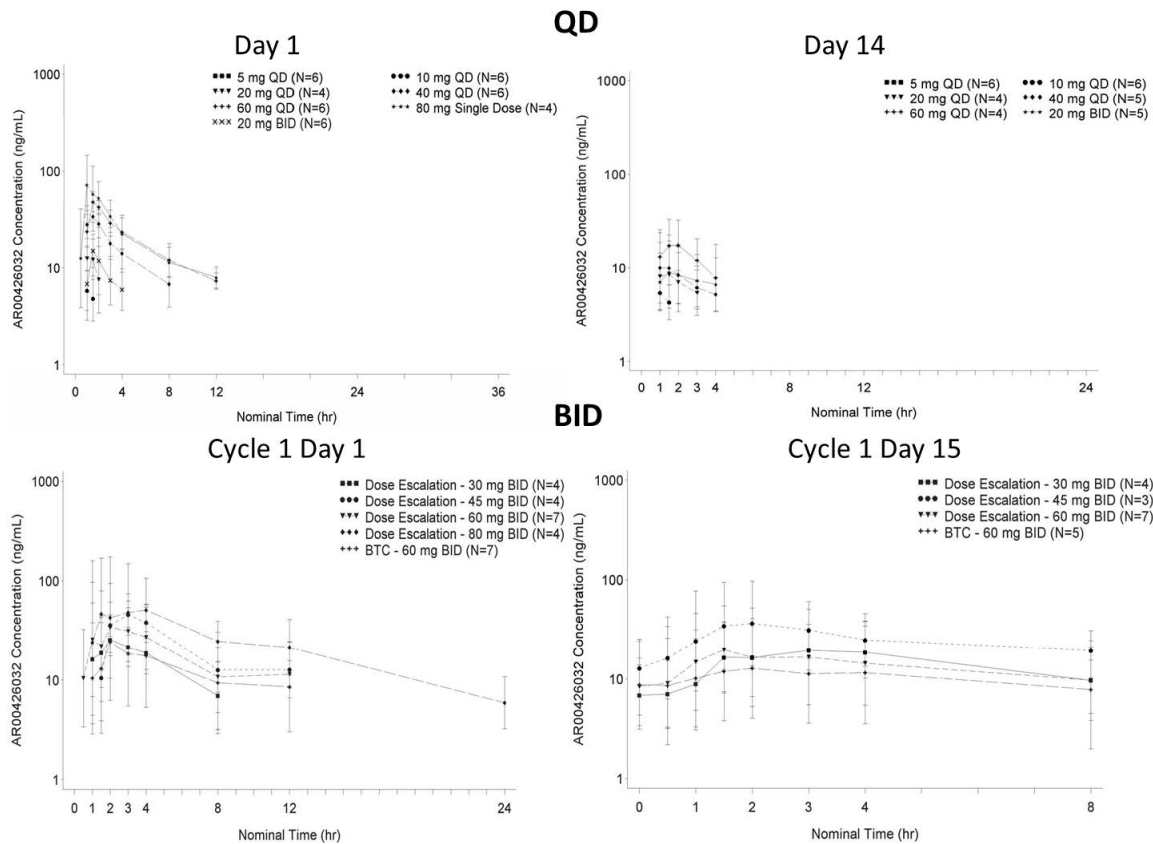
Figure 1: Geometric Mean (SD) Binimetinib Plasma Concentrations versus Time by Dose Level (Semi-logarithmic Scale)



Source: Clinical study report for Arry-162-0602, Page 550-551

Clinical study report for Arry-162-111, Page 139-140

Figure 2: Geometric Mean (SD) AR00426032 Plasma Concentrations versus Time by Dose Level (Semi-logarithmic Scale)



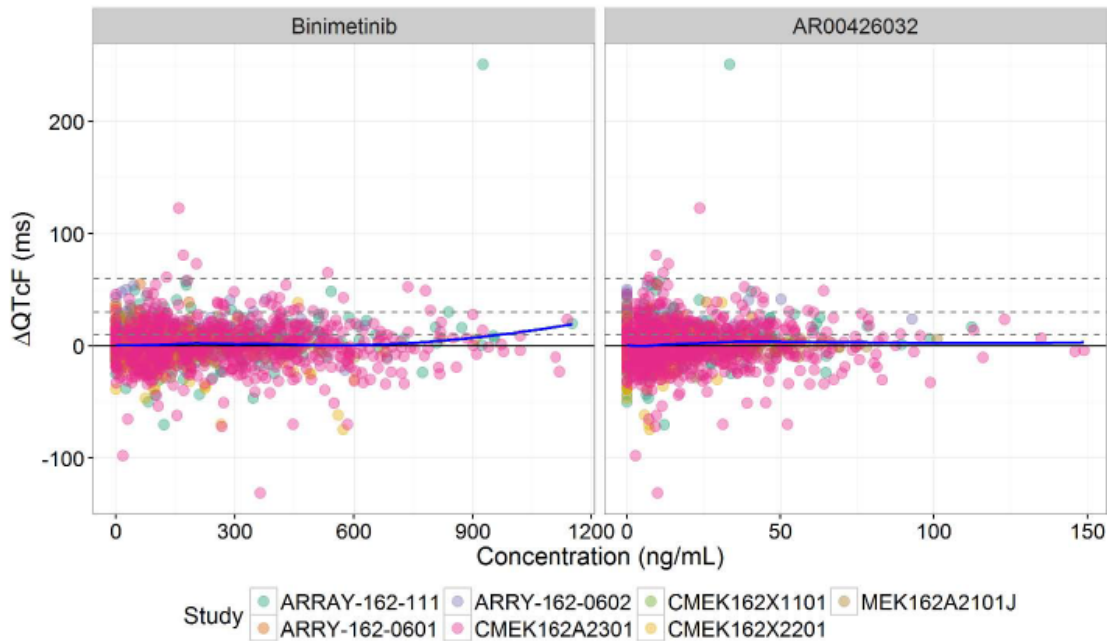
Source: Clinical study report for Arry-162-0602, Page 552-553

Clinical study report for Arry-162-111, Page 284,296

4.2.8.4.2 Exposure-Response Analysis

The concentration-QTc (C-QTc) analyses datasets included 482 subjects with a total of 1592 and 1591 time-matched ECG-concentration pairs for binimetinib and AR00426032, respectively. Based on visual inspection and the pattern of the smooth regression lines, no relationship was observed between binimetinib and AR00426032 concentrations and Δ QTcF (Figure 3).

Figure 3: Relationship between Δ QTcF and Binimetinib (Left Panel) and AR00426032 Concentrations (Right Panel)



Δ QTcF: Change from baseline in rate-corrected QT interval using Fridericia's method. The black lines represent Δ QTcF = 0 ms. The dashed grey lines represent Δ QTcF = 10 ms, 30 ms and 60 ms to reflect the E14 thresholds of concern, and the blue line is generated by a loess smooth regression.

The final binimetinib C-QTc model was a linear model with BSV on the intercept only, an effect of baseline QTcF on the intercept, and residual variability differing by study type (Sponsor's Table 4-4). BSV on the slope was removed as it didn't improve the model fitting based on AIC value. Residual variability was found to be higher for studies in patients. The general form of the model can be found below:

$$\Delta\text{QTc}_{ij} = \text{Intercept}_j + \text{Slope}_j \times \text{Conc}_{ij} + \varepsilon_{ij}$$

Modifications to the residual error model were investigated by stratifying residual error variances by study type: $\varepsilon_{ijs} \sim N(0, (\delta_s \cdot \sigma)^2)$, where ε_{ijs} is the residual error for ε_{ijs} corresponding to stratification level s , δ_s is the fold-change in standard deviation (SD) relative to the SD σ of the reference stratification level. By definition $\delta_s = 1$ for the reference stratification level.

Table 4-4. Binimetinib Concentration-QTc Final Model Estimates

Parameter	Estimate	95% CI	SE	DF	t value	Pr > t
Fixed Effects						
Intercept (ms)	0.345	(-1.07, 1.76)	0.723	1108	0.4779	0.6328
Slope (ms per ng/mL)	0.00714	(0.00414, 0.0101)	0.00153	1108	4.6733	< 0.0001
Covariate						
Δ Intercept _{QTcFB_{sln}} (ms)	-0.311	(-0.365, -0.256)	0.0278	1108	-11.1828	< 0.0001
Between-Subject Variability						
Intercept SD (ms)	12.2	(11.3, 13.3)				
Residual Unexplained Variability						
σ for Phase 1 Healthy	5.96	(5.52, 6.42)				
$\delta_{\text{Phase 1/2-Patients}}$	1.79	(1.60, 1.99)				
$\delta_{\text{Phase 3}}$	2.23	(2.02, 2.46)				

Number of subjects = 482; Number of observations = 1592.

Δ Intercept_{QTcFB_{sln}}: change in intercept for each unit change in baseline QTcF from the median value of 409 ms; Δ QTcF: change from baseline in rate-corrected QT interval using Fridericia's method; δ_s : fold-change in residual error standard deviation for stratification level S relative to reference stratification level; σ : standard deviation of residual error; CI: confidence interval; DF: degrees of freedom; Pr: probability; SD: standard deviation; SE: standard error; t: t-statistic.

Δ QTcF predictions at the mean steady-state C_{max} of Binimetinib or AR00426032 following relevant doses of binimetinib ranging from 30 to 80 mg BID as well as at extremes of the C_{max} range following the therapeutic dose of 45 mg BID was estimated by the final model in Table 4 and Table 5. The upper bound one-sided 95% CIs of Δ QTcF for the 95th and 99th percentile of steady-state C_{max} of Binimetinib following 45 mg BID binimetinib are predicted to be 6.25 and 7.28 ms. The predictions of upper bound one-sided 95% CIs of Δ QTcF for the same percentile of steady state C_{max} of AR00426032 were predicted to be 7.67 and 11.5 ms, respectively.

Table 4: Binimetinib C-QTc Model-Based Predictions of $\Delta\Delta$ QTcF by Dose Level

BID Dose (mg)	Summary Statistic	Binimetinib C_{max} (ng/mL)	Mean $\Delta\Delta$ QTcF (ms)	Upper Bound of One-Sided 95% CI (ms)
30	Mean	286	2.04	2.76
45	Mean	425	3.03	4.10
60	Mean	519	3.70	5.01
80	Mean	630	4.50	6.08
45	95 th percentile	648	4.62	6.25
45	99 th percentile	755	5.39	7.28

$\Delta\Delta$ QTcF: Placebo-corrected change from baseline in rate-corrected QT interval using Fridericia's method; BID: twice daily; CI: confidence interval; C_{max} : maximum concentration; C-QTc: concentration-corrected QT.

Table 5: AR00426032 C-QTc Model-Based Predictions of $\Delta\Delta\text{QTcF}$ by Dose Level

BID Dose (mg)	Summary Statistic	AR00426032 C_{max} (ng/mL)	Mean $\Delta\Delta\text{QTcF}$ (ms)	Upper Bound of One-Sided 95% CI (ms)
30	Mean	22.3	1.58	2.11
45	Mean	39.3	2.78	3.71
60	Mean	42.6	3.01	4.02
80	Mean	89.6	6.34	8.46
45	95 th percentile	81.2	5.74	7.67
45	99 th percentile	122	8.63	11.5

$\Delta\Delta\text{QTcF}$: Placebo-corrected change from baseline in rate-corrected QT interval using Fridericia's method; BID: twice daily; CI: confidence interval; C_{max} : maximum concentration; C-QTc: concentration-corrected QT.

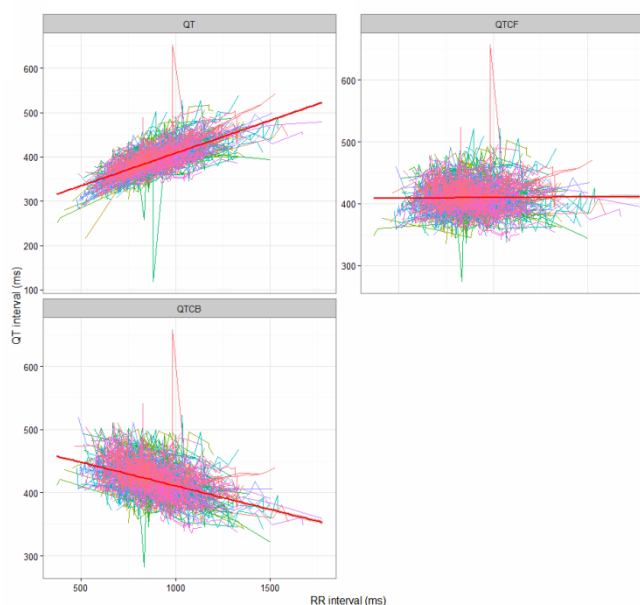
5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

This review did not evaluate of the QT/RR correction method because the sponsor only provided QTcB and QTcF correction intervals. This reviewer chose to present QTcF for the primary statistical analysis.

The relationship between different correction methods and RR is presented in Figure 4.

Figure 4: QT, QTCB and QTcF vs. RR (Each Subject's Data Points Are Connected with A Line)



5.2 STATISTICAL ASSESSMENTS

For central tendency sensitivity analysis, we focused on the data from ARRAY-162-111 study included the suprathreshold dose of 60 mg BID and had replicate ECG measurement around Tmax at the steady state. We also presented data analysis from pivotal CMEK162A2301 study which included dose at 45 mg BID.

5.2.1 QTc Analysis

5.2.1.1 The Central Tendency Analysis for Binimetinib

The primary endpoint is change from baseline in QTcF. The descriptive statistics are listed in Table 6, Table 7 and Table 8. Tables present the summary statistics (mean and standard deviation) and the 90% confidence interval for the means binimetinib dosed-escalated ranging 30 mg BID to 80 mg BID. Using central tendency analysis, the largest upper bounds of the 2-sides 90% CIs for mean dose-pooled 45 mg BID and 60 mg BID are all above 10 ms.

Table 6: Analysis Results of Δ QTcF with Largest Upper Bound for Binimetinib by Dose Level (ARRAY-162-111)

BID Dose (mg)	Total N	Visit	Time	Mean	Std Dev	90% CI for Mean
30	3	CYCLE 2 DAY 1	0	-3.0	13.3	(-25.3, 19.3)
45	44	CYCLE 2 DAY 1	1.5	4.7	18.6	(-1.1, 10.5)
60	34	CYCLE 2 DAY 1	0	4.8	23.2	(-2.0, 11.5)
80	4	CYCLE 1 DAY 1	1.5	3.7	12.2	(-10.6, 18.1)

Table 7: Analysis Results of Δ QTcF for Binimetinib Dosed from 30 mg BID to 80 mg BID (Pooled Dose Level by Visit and Time, ARRAY-162-111)

Doses	N	Visit	Time	Mean	Std Dev	90% CI for Mean
30	4	CYCLE 1 DAY 1	1.5	7.8	6.2	(0.6, 15.0)
	4	CYCLE 1 DAY 8	0	3.9	8.6	(-6.2, 14.0)
	4	CYCLE 1 DAY 8	1.5	4.3	3.1	(0.7, 7.9)
	4	CYCLE 1 DAY 15	0	5.0	7.2	(-3.6, 13.5)
	4	CYCLE 1 DAY 15	1.5	10.1	7.5	(1.3, 19.0)
	3	CYCLE 2 DAY 1	0	-3.0	13.3	(-25.3, 19.3)
45	2	CYCLE 2 DAY 1	1.5	-8.5	0.5	(-10.7, -6.2)
	44	CYCLE 1 DAY 1	1.5	0.3	16.5	(-3.9, 4.5)
	37	CYCLE 1 DAY 8	0	-0.4	18.4	(-5.5, 4.7)
	38	CYCLE 1 DAY 8	1.5	4.4	14.5	(0.4, 8.4)
	36	CYCLE 1 DAY 15	0	-1.4	19.0	(-6.7, 4.0)
	34	CYCLE 1 DAY 15	1.5	3.1	17.8	(-2.1, 8.3)
	33	CYCLE 2 DAY 1	0	-0.5	19.5	(-6.2, 5.3)
	30	CYCLE 2 DAY 1	1.5	4.7	18.6	(-1.1, 10.5)
	40	CYCLE 1 DAY 1	1.5	3.0	9.3	(0.5, 5.5)
	31	CYCLE 1 DAY 8	0	2.5	13.8	(-1.7, 6.7)
60	34	CYCLE 1 DAY 8	1.5	5.5	16.5	(0.7, 10.2)
	35	CYCLE 1 DAY 15	0	2.1	12.2	(-1.4, 5.6)
	34	CYCLE 2 DAY 1	0	4.8	23.2	(-2.0, 11.5)
	30	CYCLE 2 DAY 1	1.5	4.2	12.9	(0.2, 8.2)
	4	CYCLE 1 DAY 1	1.5	3.7	12.2	(-10.6, 18.1)
	3	CYCLE 1 DAY 8	0	-5.3	2.4	(-9.3, -1.3)
80	3	CYCLE 1 DAY 15	0	3.9	7.6	(-8.9, 16.6)
	3	CYCLE 2 DAY 1	0	-6.5	15.1	(-32.1, 19.0)
	3	CYCLE 2 DAY 1	1.5	-1.7	9.8	(-18.2, 14.8)

Table 8: Analysis Results of Δ QTcF for Binimetinib 45 mg BID by Visit and Time Level (CMEK162A2301)

Visit	Time	N	Mean	Std Dev	90% CI for Mean
Week 1 Day 1	1.5	230	0.2	16.4	(-1.6, 2.0)
> Week 1 Day 1	0	1209	-4.1	20.0	(-5.0, -3.1)
	1.5	296	0.1	20.3	(-1.9, 2.0)

5.2.1.2 Assay Sensitivity Analysis

No assay sensitivity analysis performed in this study because no positive control arm included.

5.2.1.3 Categorical Analysis

Table 9 list the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and > 500 ms. Two subject's QTcF are above 480 ms.

Table 9: Categorical Analysis for QTcF

BID Dose (mg)	Total N	Value ≤ 450 ms	450 ms < Value ≤ 480 ms	480 ms < Value ≤ 500 ms	Value > 500 ms
DE 30 mg BID	4	4	0	0	0
BRAF 45 mg BID	15	14	1	0	0
DE 45 mg BID	4	2	2	0	0
KRAS 45 mg BID	25	20	4	1	0
DE 60 mg BID	7	7	0	0	0
Biliary 60 mg BID	28	22	4	0	2
KRAS 60 mg BID	6	5	1	0	0
DE 80 BID	4	3	1	0	0
Total	93	77	13	1	2

Table 10 lists the number of subjects changes from baseline QTc ≤ 30 ms, between 30 and 60 ms, and > 60 ms. Two subjects have change from baseline are above 60 ms.

Table 10: Categorical Analysis of Δ QTcF

BID Dose (mg)	Total N	Value$\leq$30 ms	30 ms<Value$\leq$60 ms	Value>60 ms
DE 30 mg BID	4	4	0	0
BRAF 45 mg BID	15	15	0	0
DE 45 mg BID	4	3	1	0
KRAS 45 mg BID	25	22	3	0
DE 60 mg BID	7	7	0	0
Biliary 60 mg BID	28	23	3	2
KRAS 60 mg BID	6	5	1	0
DE 80 BID	4	3	1	0
Total	93	83	8	2

5.2.2 HR Analysis

The primary endpoint is change from baseline in HR. The descriptive statistics are listed in Table 11, Table 12 and Table 13. Tables present the summary statistics (mean and standard deviation) and the 90% confidence interval for the means at the therapeutic dose 45 mg BID and 60 mg BID. Using central tendency analysis, the largest upper bounds of the 2-sides 90% CIs for differences binimetinib pooled-dose at 45 mg BID and 60 mg BID are all below 10 bpm. The categorical analysis of HR presented in Table 14. Three subjects who experienced HR interval greater than 100 bpm are in binimetinib doses of 45 mg BID and 60 mg BID groups.

Table 11: Analysis Results of Δ HR with Largest Upper Bound for Binimetinib by Dose Level (ARRAY-162-111)

BID Dose (mg)	Total N	Visit	Time	Mean	Std Dev	90% CI for Mean
45	44	CYCLE 1 DAY 1	1.5	-2.0	7.0	(-3.8, -0.2)
60	34	CYCLE 2 DAY 1	0	-0.6	9.6	(-3.4, 2.1)

Table 12: Analysis Results of Δ HR for Binimetinib Dosed from 30 mg BID to 80 mg BID (Pooled Dose Level by Visit, ARRAY-162-111)

Doses	N	Visit	Time	Mean	Std Dev	90% CI for Mean
45	44	CYCLE 1 DAY 1	1.5	-2.0	7.0	(-3.8, -0.2)
	37	CYCLE 1 DAY 8	0	-4.5	7.3	(-6.6, -2.5)
	38	CYCLE 1 DAY 8	1.5	-7.1	7.8	(-9.2, -4.9)
	36	CYCLE 1 DAY 15	0	-3.9	9.9	(-6.7, -1.1)
	34	CYCLE 1 DAY 15	1.5	-7.8	9.3	(-10.5, -5.1)
	33	CYCLE 2 DAY 1	0	-3.6	9.0	(-6.2, -0.9)
60	30	CYCLE 2 DAY 1	1.5	-5.2	9.0	(-8.0, -2.4)
	40	CYCLE 1 DAY 1	1.5	-3.0	6.7	(-4.8, -1.2)
	31	CYCLE 1 DAY 8	0	-2.0	6.7	(-4.0, 0.1)
	34	CYCLE 1 DAY 8	1.5	-3.4	7.8	(-5.6, -1.1)
	35	CYCLE 1 DAY 15	0	-3.0	8.0	(-5.3, -0.7)
	30	CYCLE 1 DAY 15	1.5	-4.4	7.6	(-6.8, -2.1)
	34	CYCLE 2 DAY 1	0	-0.6	9.6	(-3.4, 2.1)
	30	CYCLE 2 DAY 1	1.5	-2.6	9.1	(-5.4, 0.2)

Table 13: Analysis Results of Δ HR for Binimetinib 45 mg BID by Visit and Time Level (CMEK162A2301)

Visit	Time	N	Mean	Std Dev	90% CI for Mean
Week 1 Day 1	1.5	230	-1.8	9.4	(-2.8, -0.8)
> Week 1 Day 1	0	1213	-1.8	11.5	(-2.3, -1.2)
	1.5	294	-3.0	12.3	(-4.1, -1.8)

Table 14: Categorical Analysis for HR

BID Dose (mg)	Total N	HR <= 100 bpm	HR >100 bpm
DE 30 mg BID	4	4	0
BRAF 45 mg BID	15	15	0
DE 45 mg BID	4	4	0
KRAS 45 mg BID	25	24	1
DE 60 mg BID	7	7	0
Biliary 60 mg BID	28	26	2
KRAS 60 mg BID	6	6	0
DE 80 BID	4	4	0
Total	93	83	3

5.2.3 PR Analysis

The primary endpoint is change from baseline in PR. The descriptive statistics are listed in Table 15, Table 16 and Table 17. Tables present the summary statistics (mean and standard deviation) and the 90% confidence interval for the means at the doses of 45 mg BID and 60 mg BID. Using central tendency analysis, the largest upper bounds of the 2-sides 90% CIs for mean differences binimetinib dosed-pooled at 45 mg BID and 60 mg BID are all above 10 ms. The categorical analysis of PR presented in Table 18. Sixteen subjects who experienced PR interval greater than 200 ms are in binimetinib dosed-groups.

Table 15: Analysis Results of Δ PR with Largest Upper Bound for Binimetinib by Dosed Level (ARRAY-162-111)

BID Dose (mg)	Total N	Visit	Time	Mean	Std Dev	90% CI for Mean
45	34	CYCLE 1 DAY 15	1.5	14.6	17.3	(9.5, 19.6)
60	29	CYCLE 1 DAY 15	1.5	11.6	14.4	(7.0, 16.1)

Table 16: Analysis Results of Δ PR for Binimetinib Dosed from 30 mg BID to 80 mg BID, (Pooled Dose Level by Visit, ARRAY-162-111)

Doses	N	Visit	Time	Mean	Std Dev	90% CI for Mean
45	44	CYCLE 1 DAY 1	1.5	4.9	9.6	(2.4, 7.3)
	36	CYCLE 1 DAY 8	0	11.8	12.4	(8.3, 15.3)
	38	CYCLE 1 DAY 8	1.5	15.7	11.3	(12.6, 18.8)
	36	CYCLE 1 DAY 15	0	8.8	18.0	(3.7, 13.9)
	34	CYCLE 1 DAY 15	1.5	14.6	17.3	(9.5, 19.6)
	33	CYCLE 2 DAY 1	0	7.5	11.9	(4.0, 11.0)
60	30	CYCLE 2 DAY 1	1.5	11.2	10.2	(8.0, 14.3)
	40	CYCLE 1 DAY 1	1.5	3.0	7.4	(1.0, 5.0)
	31	CYCLE 1 DAY 8	0	6.5	13.2	(2.4, 10.5)
	34	CYCLE 1 DAY 8	1.5	10.0	15.2	(5.6, 14.5)
	35	CYCLE 1 DAY 15	0	8.5	13.6	(4.6, 12.4)
	29	CYCLE 1 DAY 15	1.5	11.6	14.4	(7.0, 16.1)
	34	CYCLE 2 DAY 1	0	5.0	13.8	(1.0, 9.0)
	30	CYCLE 2 DAY 1	1.5	7.9	16.9	(2.7, 13.1)

Table 17: Analysis Results of Δ PR for Binimetinib 45 mg BID by Visit and Time Level (CMEK162A2301)

Visit	Time	N	Mean	Std Dev	90% CI for Mean
Week 1 Day 1	1.5	211	-0.6	19.7	(-2.8, 1.7)
> Week 1 Day 1	0	1102	11.2	28.0	(9.9, 12.6)
	1.5	271	8.1	23.0	(5.8, 10.4)

Table 18: Categorical Analysis for PR

BID Dose (mg)	Total N	PR ≤ 200 ms	PR >200 ms
DE 30 mg BID	4	4	0
BRAF 45 mg BID	15	14	1
DE 45 mg BID	4	2	2
KRAS 45 mg BID	25	21	4
DE 60 mg BID	7	6	1
Biliary 60 mg BID	28	22	6
KRAS 60 mg BID	6	5	1
DE 80 BID	4	3	1
Total	93	77	16

5.2.4 QRS Analysis

The primary endpoint is change from baseline in QRS. The descriptive statistics are listed in Table 19 and Table 20. Tables present the summary statistics (mean and standard deviation) and the 90% confidence interval for the means at the doses of 45 mg BID and 60 mg BID. Using central tendency analysis, the largest upper bounds of the 2-sides 90% CIs for the mean differences Binimetinib pooled-dose at 45 mg BID and 60 mg BID are all below 10 ms. The categorical analysis of QRS is presented in Table 21. Eight subjects who experienced QRS interval greater than 110 ms are in Binimetinib dose of 45 mg BID and 60 mg BID groups.

Table 19: Analysis Results of ΔQRS with Largest Upper Bound for Binimetinib by Dose Level (ARRAY-162-111)

BID Dose (mg)	Total N	Visit	Time	Mean	Std Dev	90% CI for Mean
45	44	CYCLE 1 DAY 15	1.5	4.1	7.5	(1.9, 6.2)
60	34	CYCLE 1 DAY 15	0	4.1	6.6	(2.2, 6.0)

Table 20: Analysis Results of Δ QRS for Binimetinib Dosed from 30 mg BID to 80 mg BID, (Pooled Dose Level by Visit, ARRAY-162-111)

BID Dose Mg	N	Visit	Time	Mean	Std Dev	90% CI for Mean
45	44	CYCLE 1 DAY 1	1.5	-0.0	3.1	(-0.8, 0.8)
	37	CYCLE 1 DAY 8	0	3.2	6.4	(1.4, 4.9)
	38	CYCLE 1 DAY 8	1.5	3.0	6.4	(1.2, 4.7)
	36	CYCLE 1 DAY 15	0	3.9	7.5	(1.8, 6.0)
	34	CYCLE 1 DAY 15	1.5	4.1	7.5	(1.9, 6.2)
	33	CYCLE 2 DAY 1	0	3.9	7.6	(1.7, 6.2)
	30	CYCLE 2 DAY 1	1.5	3.4	8.8	(0.7, 6.1)
	40	CYCLE 1 DAY 1	1.5	0.9	4.5	(-0.3, 2.1)
60	31	CYCLE 1 DAY 8	0	2.3	6.1	(0.5, 4.2)
	34	CYCLE 1 DAY 8	1.5	1.4	5.1	(-0.0, 2.9)
	35	CYCLE 1 DAY 15	0	4.1	6.6	(2.2, 6.0)
	30	CYCLE 1 DAY 15	1.5	3.8	5.2	(2.2, 5.4)
	34	CYCLE 2 DAY 1	0	3.0	6.1	(1.2, 4.8)
	30	CYCLE 2 DAY 1	1.5	3.1	5.3	(1.4, 4.7)

Table 21: Categorical Analysis for QRS

BID Dose (mg)	Total N	QRS $\leq$ 110 ms	QRS $>$ 110 ms
DE 30 mg BID	4	4	0
BRAF 45 mg BID	15	15	0
DE 45 mg BID	4	3	1
KRAS 45 mg BID	25	22	3
DE 60 mg BID	7	6	1
Biliary 60 mg BID	28	26	2
KRAS 60 mg BID	6	5	1
DE 80 BID	4	4	0
Total	93	85	8

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean concentration-time profiles for binimetinib and the metabolite AR00426032 are illustrated in Figure 1 and Figure 2.

The relationships between ΔQ_{Tc} and binimetinib or the metabolite AR00426032 were investigated separately by linear mixed-effects modeling with $Q_{Tc}F$ change from baseline ($\Delta Q_{Tc}F$) as the dependent variable. The final C- Q_{Tc} model was a linear model with random effect on the intercept only, an effect of baseline $Q_{Tc}F$ and Study on the intercept, and residual variability differing by study type. Including study as categorical factors on the intercept in the final model was able to fit data better (based on AIC value) compared to the model proposed by the sponsor.

According to the final model, a significant but relatively flat relationship between $\Delta Q_{Tc}F$ and binimetinib concentrations was observed (with a slope estimate of 7.43 ms/(ug/ml), $p < 0.0001$) (Figure 5). Based on the final model, the mean (90% CI) $\Delta Q_{Tc}F$ at mean steady-state C_{max} of 0.425 ug/ml following therapeutic dosing regimen 45 mg BID is predicted to be 3.22 (1.31, 5.13) ms, and the corresponding predictions of $\Delta Q_{Tc}F$ for the 95th percentile of steady-state C_{max} of 0.648 ug/ml is 4.88 (2.71, 7.04) ms. Similar C- Q_{Tc} linear model was built for the metabolite AR00426032 (Figure 6). The model predictions of $\Delta Q_{Tc}F$ for the 95th percentile of steady-state C_{max} (0.081 ug/ml) of metabolite AR00426032 following 45 mg BID is also predicted to be < 10 ms (6.09 ms with 95% CI: 4.16, 8.03 ms).

Figure 5: $\Delta Q_{Tc}F$ vs. Binimetinib Concentration

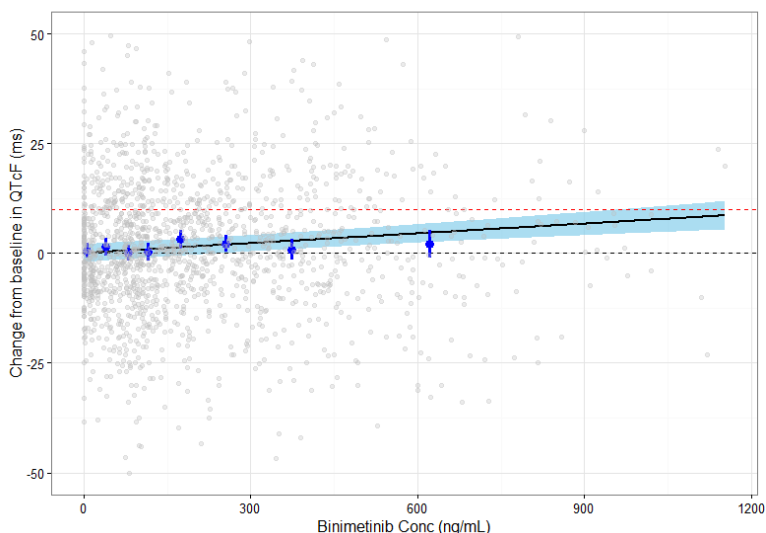
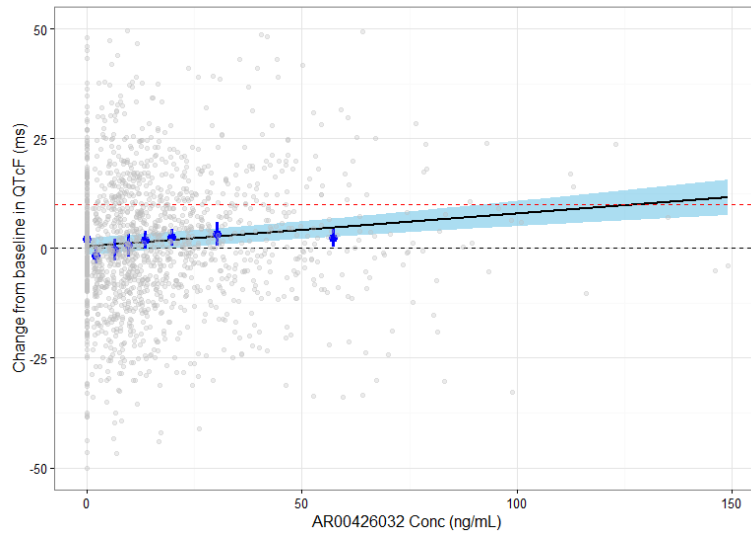
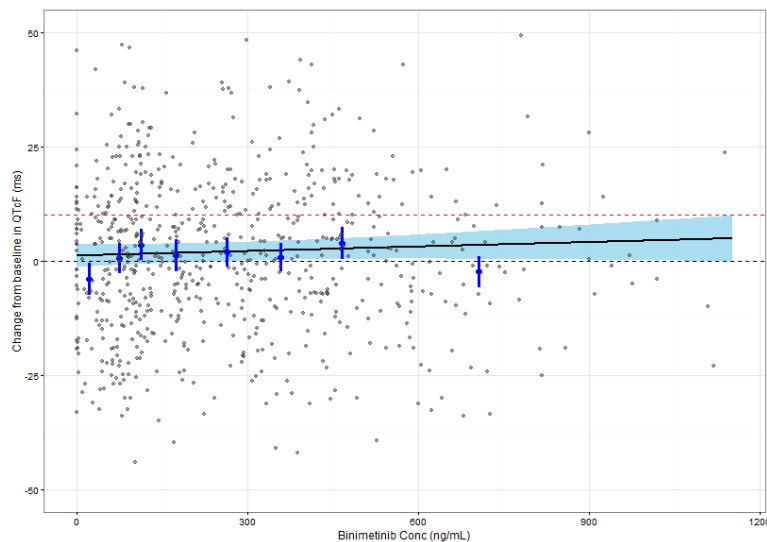


Figure 6: Δ QTcF vs. AR0026032 Concentration



A separate C-QT analysis was also conducted in study A2301 only because it provided majority of concentration-QTc data for the therapeutic dose (706 out of 1592 (43%) time-matched C-QT pairs was collected from study A2301). A non-significant relationship between Δ QTcF and binimetinib concentrations was observed (with a slope estimate of 3.28 ms/(ug/ml), $p=0.2159$). The mean (90% CI) Δ QTcF at mean steady-state C_{max} of 0.425 ug/ml following therapeutic dosing regimen 45 mg BID is predicted to be 2.55 (0.38, 4.72) ms (Figure 7).

Figure 7: Δ QTcF vs. Binimetinib Concentration in Study A2301



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

The sponsor's safety evaluation of the pooled data is presented in Section 4.2.8.3.

5.4.2 ECG assessments

Digital ECGs from Study ARRAY-162-111 and the pivotal Study CMEK162A2301 are not submitted. However, ECG acquisition and interpretation in two small studies with digital ECGs submitted (1101, 2201) appears acceptable.

5.4.3 PR and QRS Interval

No clinically relevant effects on PR and QRS.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure	Maximum proposed clinical dosing regimen from the Phase 3, randomized trial in patients with advanced unresectable or metastatic NRAS mutation-positive cutaneous melanoma (CMEK162A2301): 45 mg BID Mean exposure from the Phase 2 study in patients with advanced and unresectable or metastatic cutaneous melanoma harboring a BRAF V600E or NRAS mutation (CMEK162X2201) at 45 mg dose: C_{max}: 458 ng/mL (46.1%) AUC_{tau}: 1648 hr*ng/mL (35.3%) $C_{max,ss}$: 439 ng/mL (53.9%) $AUC_{tau,ss}$: 2103 hr*ng/mL (38.3%) Source: CMEK162X2201 CSR, Table 11-11	
Maximum tolerated dose	60 mg BID (ARRAY-162-111) Source: SCE, Section 4.3	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	80 mg (ARRAY-162-111)
	Multiple Dose	80 mg BID (ARRAY-162-111, dose nontolerable) 60 mg BID (CMEK162X2201) Source: SCE, Section 4.3
Exposures Achieved at Maximum Tested Dose	Single Dose	80 mg (ARRAY-162-111 Cycle 1 Day 1) C_{max}: 687 ng/mL (66.6%) AUC_{tau}: 2960 hr*ng/mL (37.4%) Source: ARRAY-162-111 CSR, Table 14
	Multiple Dose	No exposure data acquired at 80 mg BID (ARRAY-162-111) 60 mg BID (Cycle 1 Day 15) $C_{max,ss}$: 512 (30.8%) – 594 ng/mL (68.8%) Source: SCP, Table 3-5, studies ARRAY-162-111, CMEK162X1101 and CMEK162X2201 $AUC_{tau,ss}$: 2637 hr*ng/mL (20.8%) Source: SCP, Table 3-5, study CMEK162X2201
Range of linear PK	Binimetinib exposure was dose-proportional over the dose ranges analyzed in studies ARRAY-162-0601, ARRAY-162-0602 and ARRAY-162-111	

	Source: SCP, Section 3.1.3 Linearity Factor (LF) following 5, 10, 20, 40, 60 mg QD and 20 mg BID (ARRAY-162-0602): 0.893 (13.3) to 1.23 (35.5) Source: SCP, Table 3-5	
Accumulation at steady state	R _{AUC} : 0.926 (10.4) to 2.50 (NC) across all doses and dosing regimens (5, 10, 20, 40, 60 mg QD or 20, 30, 45, 60 mg BID) Source: SCP, Table 3-5	
Metabolites	The most abundant metabolites produced from human hepatocyte incubations were products of direct glucuronidation of binimetinib. Additional metabolites detected include an amide formed by cleavage of the N-O bond in the aliphatic side chain (b) (4) and an N-desmethylated entity (active metabolite AR00426032 or M3). The maximum contribution of direct glucuronidation to the clearance of binimetinib was estimated to have been 61.2%. Following a single oral dose of 45 mg [¹⁴ C] binimetinib in healthy subjects, approximately 60% of the circulating radioactivity AUC in plasma was attributable to binimetinib. In vitro, CYP1A2 and CYP2C19 catalyzes the formation of the active metabolite, which represents < 20% of the binimetinib exposure clinically. Source: CMEK162A2102 CSR, Section 11.4.3.6 and Section 11.4.3.2, DMPK R1200493	
Absorption	Absolute/Relative Bioavailability	Based on human ADME study, oral absorption is estimated to be at least 50% Source: CMEK162A2102 CSR, Section 13
	T _{max}	Approximately 1.5 hours across studies and has ranged from 0 to 8 hours Source: SCP
Distribution	V _d /F or V _d	Human ADME mean (%CV) V _z /F = 384 L (29.3%) Source: CMEK162A2102 CSR, Table 11-6
	% bound	97.2% (96.5 – 97.7) Source: DMPK R1100217, Section 3.2
Elimination	Route	After a single oral dose of 45 mg of ¹⁴ C-binimetinib, a mean of 62.3% of the radioactivity dose was eliminated in the feces, while 31.4% was eliminated in the urine. In urine, 6.5% of the radioactivity dose was excreted as binimetinib. The estimated mean CL _R value of 1.78 L/hr accounted for 6.3% of the total mean CL/F value of 28.2 L/hr. Source: CMEK162A2102 CSR, Section 11.4.3.3.2 and 11.4.4
	Terminal t _{1/2}	The median (range) binimetinib terminal half-life (T _{1/2}) was 8.66 hours (8.10 to 13.6 hours) Source: CMEK162A2102 CSR, Section 11.4.2
	CL/F or CL	Human ADME mean (%CV) CL/F = 28.2 L/hr (17.9%) Source: CMEK162A2102 CSR, Table 11-6
Intrinsic Factors Source: Module 2.7.2	Age	No clinically significant correlation between age (range 27 – 74 years) and CL/F based on population PK analysis. Volume tended to decrease modestly with age.

	Sex	No clinically significant differences in PK (<20% based on population PK analysis)
	Race	No substantial trends observed for CL/F versus race based on population PK analysis. Exposure in Japanese tends to be ~1.5- to 2-fold higher than non-Japanese.
	Hepatic & Renal Impairment	AUCs in patients with mild and moderate renal impairment were 18% and 34% greater than patients without renal impairment based on population PK analysis. An assessment of exposure changes in severely impaired patients is on-going as part of a renal impairment study. Increases in C_{max} and AUC in patients with mild hepatic impairment were modest (14% and 3%, respectively) based on an on-going hepatic impairment study. C_{max} and AUC were ~2-fold higher in patients with moderate hepatic impairment. An assessment of exposure changes in severely impaired patients is on-going as part of a hepatic impairment study.
Extrinsic Factors	Drug interactions	After a lead-in period of 1 week with binimetinib, AUC₀₋₂₄ of midazolam was 12% lower, and C_{max} of midazolam was 26.7% lower than when administered as a single dose. This decrease was reversed after a lead-in period of 2 weeks with binimetinib. The same trend was observed with 1-hydroxymidazolam, leading to metabolic ratios that were constant between periods, which is not compatible with any increased metabolic activity. The other marker of induction, 4β-hydroxycholesterol, displayed similar levels across periods. The changes in exposure between periods were either similar to or lower than the overall variability observed within the same period for AUC and C_{max} suggesting that these fluctuations are not likely to be clinically relevant. Source: CMEK162A2105 CSR Co-administration of binimetinib with multiple oral once-daily doses of 20 mg rabeprazole had no effect on the extent of exposure to binimetinib and AR00426032, however, C_{max} values of binimetinib and AR00426032 were both lower (17% and 24% lower, respectively). There were no differences in relative median T_{max} between the 2 treatments and the differences in C_{max} were within the between subject variability observed. While these decreases in C_{max} values for both analytes indicate that PPI co-administration decreases the rate of binimetinib

		absorption and AR00426032 formation, these differences are not likely to be clinically relevant. Source: ARRAY-162-105 CSR
	Food Effects	The results of this trial showed that there was a mild effect of food on the peak plasma concentrations of binimetinib. Compared to fasted conditions, the low-fat meal increased the estimated geometric mean C_{max} of binimetinib by about 29% on average while the high-fat meal decreased it by about 17% on average. The time of the peak concentration (T_{max}) was increased in both cases (more notably after a high-fat meal), suggesting that food delayed the absorption of binimetinib in the systemic circulation. Regarding AUCs, mean values remained unchanged between conditions even though some variations were observed between periods, however, without any identifiable trend or pattern. This suggested that the amount of binimetinib absorbed in the systemic circulation was similar when administered with or without food. The effect of food was therefore limited to the absorption rate. The magnitude of the changes in C_{max} observed in fed conditions was similar to or smaller than the variability observed on this parameter in all treatment conditions. Also, variability of primary PK parameters (C_{max} and AUCs) was lower after food intake than in the fasted state. These two observations suggested that the mild effect of food on the absorption kinetics of binimetinib is not clinically relevant Source: CMEK162A2103 CSR
Expected High Clinical Exposure Scenario	Binimetinib has been studied at doses up to 80 mg, and has been shown to be dose proportional in the range of 5 – 80 mg following single dose and 30 mg to 60 mg following multiple doses. In study ARRAY-162-111 a 1.2-fold increase in C_{max} was observed at the 60 mg dose compared to the 30 mg dose. A 1.2 increase in AUC was observed at the 60 mg dose compared to the 45 mg. Two of the 3 patients receiving 80 mg binimetinib (ARRAY-162-111) experienced dose limiting toxicities and dose reduced to 60 mg. Subsequently, the third patient was also reduced to 60 mg. Steady-state exposure was not measured at the 80 mg dose.	
Preclinical Cardiac Safety	Nonclinical cardiovascular safety pharmacology studies included <i>in vitro</i> hERG evaluations for binimetinib (GLP) and an active metabolite (non-GLP), AR00426032 and an <i>in vivo</i> GLP telemetry study of binimetinib in the monkey. Binimetinib showed a 30% inhibition of the hERG channel at 30 μ M, so the IC_{50} value is > 30 μ M which supports a minimal clinical risk for QTc prolongation. AR00426032 showed a 11% inhibition of the hERG channel at 100 μ M, so the IC_{50} value is > 100 μ M, again, this supports a minimal risk for QTc prolongation. In the monkey telemetry study with binimetinib, single dose levels of 1, 3 or 10 mg/kg were evaluated. There were no changes at any dose level in systemic blood pressures (systolic,	

	diastolic, mean arterial and pulse pressure), heart rate, electrocardiographic intervals (PR, QT, QTc, QRS), body temperature or qualitative evaluation of ECG waveforms. Thus, the NOAEL for in vivo CV assessment was the top dose of 10 mg/kg. While full TK data sets were not generated in the GLP CV telemetry study, exposures from the non-GLP monkey pharmacokinetic studies, where the same dose levels were evaluated, showed the following mean C_{max} and AUC (SD in parentheses) at the same dose levels: <table><tr><td></td><td>C_{max} (µg/mL)</td><td>AUC₀₋₂₄ (h*µg/mL)</td></tr><tr><td>1 mg/kg</td><td>0.049 (0.012)</td><td>0.564 (0.030)</td></tr><tr><td>3 mg/kg</td><td>0.330 (0.239)</td><td>2.500 (0.701)</td></tr><tr><td>10 mg/kg</td><td>0.898 (0.483)</td><td>7.870 (1.390)</td></tr></table>		C _{max} (µg/mL)	AUC ₀₋₂₄ (h*µg/mL)	1 mg/kg	0.049 (0.012)	0.564 (0.030)	3 mg/kg	0.330 (0.239)	2.500 (0.701)	10 mg/kg	0.898 (0.483)	7.870 (1.390)
	C _{max} (µg/mL)	AUC ₀₋₂₄ (h*µg/mL)											
1 mg/kg	0.049 (0.012)	0.564 (0.030)											
3 mg/kg	0.330 (0.239)	2.500 (0.701)											
10 mg/kg	0.898 (0.483)	7.870 (1.390)											
Clinical Cardiac Safety	As described in Section 2.7.4, sub-section 4.2, there were seven studies involving a total of 649 subjects and patients which were pooled and which included concentration-QTcF and concentration-heart rate analyses using a linear mixed-effect (LME) model. • [CMEK162A2301] (n=383 treated): This was a two-arm, randomized, parallel group, open-label, multicenter, Phase 3 study designed to compare the efficacy and safety of binimetinib to dacarbazine in adult patients with advanced unresectable or metastatic <i>NRAS</i> mutation-positive cutaneous melanoma, or unknown primary melanoma, who were previously untreated or who had progressed on or after prior treatment with immunotherapy for unresectable or metastatic disease. Presence of the <i>NRAS</i> Q61 mutation in tumor tissue was required. This study planned to randomize patients in a 2:1 ratio to binimetinib (45 mg orally BID) or dacarbazine (1000 mg/m² IV every 3 weeks). There were N=269 patients (32 ongoing) treated in the binimetinib treatment arm and N=114 patients (10 ongoing) treated in the dacarbazine arm. • [CMEK162X2201] (n=183 treated). This was an open-label, single-arm study designed to assess the safety and efficacy of binimetinib in patients with advanced unresectable or metastatic <i>BRAF</i> or <i>NRAS</i> mutation-positive melanoma. It included patients treated at 2 dose levels of binimetinib, 45 mg BID (158 patients) and 60 mg BID (25 patients). There were N=117 patients with the <i>NRAS</i> mutation treated with 45mg BID (13 ongoing), N=41 patients (0 ongoing) with the <i>BRAF</i> mutation treated with 45mg BID, and N=25 patients (2 ongoing) with the <i>BRAF</i> mutation treated with 60mg BID of binimetinib. • [CMEK1621A2101J] (n=37 treated). This was a randomized, single-center, open-label, two-sequence, two-period crossover Phase I study. Subjects received both treatments. Subjects were randomized to one of two treatment sequences containing two treatment periods, with at least a 7-day washout between each dose. Each treatment sequence was to have 18 subjects. This was a relative bioavailability study comparing Novartis Clinical Service Form (NCSF) and Array CSF (ACSF). All subjects received 45mg binimetinib as single doses: 35 subjects												

	received 45mg single dose NCSF and 36 subjects received 45mg single dose ACSF. • [CMEK162X1101] (n= 21 treated). This was a first-in-Japanese study of MEK162 and was designed as an open label, multi-center, Phase I, dose escalation study to be conducted in two stages; 1) a dose escalation part to determine the MTD/RP2D based on safety and tolerability of MEK162 when administered orally on a twice daily (b.i.d.) continuously dosing schedule with advanced solid tumor patients, followed by 2) an expansion part to further assess the safety and preliminary anti-tumor activity with patients whose tumor harbors RAS or BRAF mutations. The decision to escalate to the next dose level was guided by following the recommendation of the adaptive Bayesian Logistic Regression Model (BLRM) for dose escalation with overdose control (EWOC) until the MTD/RP2D was defined. A total of 21 patients were enrolled; 14 patients were enrolled in the dose escalation part, of those 6 patients were enrolled in the 30mg BID dose level cohort and 8 patients were enrolled in the 45mg BID dose level cohort. Seven patients were enrolled in the expansion part at 45mg BID dose level. Overall, a total of 15 patients were treated with MEK162 at the 45mg BID dose level. • [ARRAY-162-111] (n=93 treated). This was a multicenter, open-label, Phase 1 study conducted in 2 phases: a Dose-escalation Phase followed by an Expansion Phase. The Expansion Phase included 3 cohorts: a Biliary Cancer cohort (up to approximately 25 patients with advanced or metastatic biliary cancer), a KRAS-mutant CRC cohort (up to approximately 25 patients with KRAS-mutant metastatic CRC) and a BRAF-mutant CRC cohort (up to approximately 15 patients with BRAF-mutant metastatic CRC). The Dose-escalation Phase was designed to determine the MTD and evaluate the safety profile of MEK-162 administered orally (PO) twice daily (BID) to patients with advanced solid tumors in continuous 21-day cycles. The purpose of the Expansion Phase, consisting of up to approximately 65 total patients in 3 cohorts, was to further evaluate the safety profile of ARRAY-438162, to confirm that the rate of DLTs was less than 33%, to obtain preliminary estimates of efficacy to aid in the design of subsequent Phase 2/3 studies and to further characterize the PK and PD of MEK-162. Initially, patients in each expansion cohort were to be treated at the MTD determined in the Dose-escalation Phase. A total of 19 patients were treated in the Dose-escalation Phase at the following binimetinib doses: 30mg BID (n=4), 45mg BID (n=4), 60mg BID (n=7), and 80mg BID (n=4). A total of 74 patients were treated in the Dose-expansion phase at the following doses by indication: biliary 60mg BID (n=28), KRAS CRC 60mg BID (n=6), KRAS CRC 45mg BID (n=25), and BRAF CRC 45mg BID (n=15). • [ARRAY-162-0601] (n= 25 treated). This was a Phase I, randomized, placebo-controlled, double-blind, dose escalation study to assess
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	safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) after a single dose of MEK162 in healthy volunteers. At each dose level, subjects were randomized to receive MEK162 or placebo (vehicle; Sterile Water for Irrigation, USP) at a 4:1 ratio. Dose-escalation continued as long as each dose was well tolerated or until all planned dose cohorts were completed. A total of 20 subjects were treated with binimetinib at the following single doses: 5mg (n=4), 10 mg (n=4), 20 mg (n=4), 30 mg (n=4), and 40 mg (n=4). There were 5 subjects treated with placebo. • [ARRY-162-0602] (n=50 treated). This was a Phase I, double-blind, placebo-controlled, dose-escalation study designed to assess the safety, PK, and PD of orally administered MEK162 in healthy subjects. A total of 38 subjects were treated in the dose escalation portion of the study at the following binimetinib doses: 5 mg QD (n=6), 10 mg QD (n=6), 20 mg QD (n=4) as an oral suspension for 14 days; 20 mg BID (n=6), 40 mg QD (n=6), 60mg QD (n=6) as an oral gelatin capsule for 14 days; and, 80mg QD (n=4) as an oral gelatin capsule single dose. Electrocardiograms were performed at Screening and on study as a component of safety monitoring and are presented for the Restricted Safety Set (Studies CMEK162A2301 and CMEK162X2201). Full descriptions of the ECG findings from all studies within the Broad Safety Set are provided in the individual study CSRs (Module 5). Notable abnormalities in ECG measurements were summarized for patients who had baseline and post-baseline values and who were considered to be “at risk” of a given abnormality at baseline, i.e., their baseline values did not meet the criteria for the abnormality. For the analysis of change from baseline (e.g., increase from baseline by a certain amount), all patients with baseline and post-baseline values were included. If ECGs were performed in duplicate or triplicate at screening, the baseline value was the average of all available ECG measurements on the last assessment prior to the start of study treatment. Data from the seven pooled studies evaluated concentration-QTcF and concentration-heart rate analyses using a linear mixed-effect (LME) model. In total, QTcF prolongation > 500 ms occurred in 1.1% (7 of 649) of evaluable subjects and QTcF increased by ≥ 60 ms from baseline in 2.0% (13 of 649) of evaluable subjects. At the mean predicted steady-state C_{max} following 45 mg BID, the model predicted mean placebo-corrected change from baseline QTcF ($\Delta\Delta$QTc) and model predicted mean placebo-corrected change from baseline heart-rate ($\Delta\Delta$HR) were 3.03 ms and -1.26 bpm, respectively, indicating no clinically meaningful QT prolongation or heart rate changes at the therapeutic dose. Details on these analyses can be found in the Summary of Clinical Pharmacology (Module 2.7.2) and the binimetinib cardiac safety analysis Report CP16-002 (Module 5.3.3.5). Table 4-2 in Section 2.7.4 presents a summary of notably abnormal ECG values for the Restricted Safety Set. Throughout this section, percentages
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were calculated using a denominator that represents the number of patients with values that did not meet the criteria for a given abnormality at baseline.

Increased QT intervals were the most common ECG abnormality observed. When QT interval was corrected using Bazett's formula (QTcB), 29.0% and 35.3% of patients in the binimetinib and dacarbazine arms of Study CMEK162A2301, respectively, experienced increases from baseline of > 30 ms, with increases of > 60 ms reported for 4.3% and 8.8% of patients in the binimetinib and dacarbazine arms, respectively. Categorical shifts in absolute QTcB values reflected increases to > 450 ms (30.0% of patients in the binimetinib arm vs. 31.7% of patients in the dacarbazine arm), > 480 ms (9.6% of patients in the binimetinib arm vs. 8.0% of patients in the dacarbazine arm) and > 500 ms (2.4% of patients in the binimetinib arm vs. 5.9% of patients in the dacarbazine arm) on study.

When QT interval was corrected using Fridericia's formula (QTcF), 19.5% and 22.6% of patients in the binimetinib and dacarbazine arms of Study CMEK162A2301, respectively, experienced increases from baseline of > 30 ms, with increases of > 60 ms reported for 3.4% and 4.7% of patients in the binimetinib and dacarbazine arms, respectively. Categorical shifts in absolute QTcF values reflected increases to > 450 ms (11.9% of patients in the binimetinib arm vs. 15.0% of patients in the dacarbazine arm), > 480 ms (3.8% of patients in the binimetinib arm vs. 1.9% of patients in the dacarbazine arm) and > 500 ms (1.9% of patients in the binimetinib arm vs. 0.9% of patients in the dacarbazine arm) on study.

Increases in QTcF in the all melanoma (binimetinib 45 mg) population were reported at nearly the same incidences reported in the binimetinib arm of Study CMEK162A2301, while increases in QTcB were reported for a slightly larger proportion of patients in the binimetinib arm of Study CMEK162A2301 compared with the all melanoma (binimetinib 45 mg) population.

In the Phase 3 clinical trial [CMEK162A2301] new QTcF > 500 ms was reported for 1.9% of patients at risk in the binimetinib arm and 0.9% of patients at risk in the dacarbazine arm. All of these abnormal findings were isolated events, found at a study visit, without any pattern to time of onset and without clinical implications for the patient. An increase from baseline in QTcF of > 30 ms was reported for 19.8% of patients at risk in the binimetinib arm and 23.6% of patients at risk in the dacarbazine arm and an increase from baseline in QTcF of > 60 ms was reported for 3.4% of patients at risk in the binimetinib arm and 4.7% of patients at risk in the dacarbazine arm. New heart rate of < 60 bpm was reported for more patients in the binimetinib arm as compared to the dacarbazine arm (38.8% vs. 15.3% of patients at risk, respectively), while new heart rate of > 100 bpm was reported for fewer patients in the binimetinib arm as compared to the dacarbazine arm (7.1% vs. 17.2% of patients at risk, respectively). Of the 6 patients with an AE of ECG QT prolonged reported, none had associated clinical symptoms of presyncope, syncope or loss of consciousness associated with the QT prolongation. In the binimetinib arm, QTc

prolongation events requiring dose adjustment or study drug interruption were reported for 1.1% of patients. In the dacarbazine arm, one patient (0.9%) discontinued study drug due to a QTc prolongation event. One patient in each arm had an SAE reported in this grouping; ECG QT prolonged (0.4% of patients) in the binimetinib arm and syncope (0.9% of patients) in the dacarbazine arm. In the binimetinib arm, the maximum reported severity of QTc prolongation events was grade 1 (0.7% of patients), grade 2 (1.5% of patients) and grade 3 (1.1% of patients); no grade 4 events were reported. In the dacarbazine arm, the maximum reported severity of QTc prolongation events was grade 1 (1.8% of patients) and grade 3 (1.8% of patients); no grade 2 nor 4 events were reported. In summary, an increase from baseline in QTcF of > 30 ms was reported for 19.8% of patients at risk (i.e., with non-missing values at baseline and post-baseline, and with a baseline value within normal limits) in the binimetinib arm and 23.6% of patients at risk in the dacarbazine arm and an increase from baseline in QTcF of > 60 ms was reported for 3.4% of patients at risk in the binimetinib arm and 4.7% of patients at risk in the dacarbazine arm. It was concluded that clinical evidence to date does not warrant classification of QT prolongation as an identified risk following treatment with the binimetinib doses being evaluated in this study.

In the overall analysis, there was no clear evidence of a significant increase in the QT interval with binimetinib administration relative to the control arm (dacarbazine) and no evident safety signal.

In the Phase 1 trial in Japanese patients [CMEK162X1101] no patient experienced QTcF > 480 msec, whereas 2 patients (10.0%) experienced QTcF > 450 msec. No patient experienced QTcF prolongation (QTcF increase from baseline) of > 60 msec. Seven patients (33.3%) experienced QTcB prolongation (QTcB increase from baseline of > 30 msec). No AEs related to QT prolongation were reported.

In the Phase 1 dose escalation and expansion study [ARRAY-162-111] the majority of patients had Grade 0 (≤ 450 msec; 78 patients [84%]) or Grade 1 (451 msec to 480 msec; 14 patients [15%]) mean triplicate QTcB interval values at Baseline; 1 patient (1%) had a Grade 3 (> 500 msec) QTcB interval value at Baseline. More than half of the patients remained at their Baseline grade throughout the study (66 patients [71%]), while 24 patients (26%) experienced prolongation of their QTcB interval values. One-grade increases in mean triplicate QTcB interval values from Grade 0 or Grade 1 at Baseline to Grade 1 (451 msec to 480 msec) or Grade 2 (481 msec to 500 msec) on study, respectively, occurred in 17 patients (18%). Two-grade increases in mean triplicate QTcB interval values from Grade 0 at Baseline to Grade 2 (481 msec to 500 msec) on study occurred in 4 patients (4%; 1 patient in the 45 mg BID dose group and 3 patients in the 60 mg BID dose group). A 3-grade increase in mean triplicate QTcB interval values from Grade 0 at Baseline to Grade 3 (> 500 msec) on study occurred in 3 patients (3%; 1 patient in the 30 mg BID dose group and 2 patients in the 60 mg BID dose group). Grade 1 changes from Baseline (31 msec to 60 msec) in QTcB

interval values were reported for 12 patients (13%). Five patients (5%; 1 patient in the 30 mg BID dose group and 4 patients in the 60 mg BID dose group) had a Grade 2 (> 60 msec) change from Baseline in their QTcB interval value. The incidence and severity of changes from Baseline QTcB interval values did not appear to be dose related. Clinically significant findings were summarized in Section 12.5.1.3 of the Clinical Study Report. Importantly, it was concluded that clinically significant ECG values (i.e., a ≥ 2 -grade shift from Baseline in absolute QTcB interval values and/or a shift in mean triplicate QTcB value > 60 msec) were reported in 8% of patients and did not appear to be dose related.

In the Phase 1 study [CMEK1621A2101J] there were no notable new or worsening abnormalities in QTcF. Reported values observed with QT and QTcB intervals were: QT interval increase of > 30 msec reported in three subjects (8.1%); new abnormal QT of > 450 msec reported in one subject (2.8%); QTcB increase of > 30 msec reported in two subjects (5.4%); new abnormal QTcB > 450 msec reported in one subject (2.7%). The Investigator did not consider any of these findings to be AEs.

In the Phase 1 study [ARRY-162-0601] five subjects experienced increases of 30 - 59 msec from baseline QTc intervals. Range of the increases from baseline was 30 - 38 msec and did not follow any treatment or dose related trends. No medically important trends were observed with respect to ECG parameters regarding subject safety.

In the Phase 1 study [ARRY-162-0602] it was noted that although the 40 mg and 60 mg ARRY-438162 QD dose groups exhibited slight increases in the mean QT interval compared to baseline from Day 1 to Day 14, as well as the 80 mg MEK162 single-dose group from Day 1 to Day 2, there were no clear dose-related trends in mean QT interval.

Overall, mean QTcB intervals either decreased from baseline or increased minimally for all groups at postdose time points. No clear treatment-related trend was observed with respect to MEK162 dose level. The largest mean QTcF interval increases from baseline for the multiple-dose groups were exhibited by the 60 mg MEK162 QD group on Day 1 (+8.3 msec) and Day 8 (+13.4 msec). However, the actual mean QTcF intervals at these time points were 396.8 and 392.8 msec, respectively. The 80 mg MEK162 single-dose group exhibited a +12.3 msec increase from baseline on Day 1 (to 397.7 msec). There were no clear treatment-related or dose-related trends observed regarding individual maximal QT, QTcB, or QTcF intervals. Overall, no treatment- or dose-related trends were observed with respect to ECG parameters. There were no ECG AEs reported in this study. The Investigator considered all individual abnormal ECG results to be not clinically significant.

In the overall analysis across the pooled studies, there was no clear evidence of a significant increase in the QT interval with binimetinib administration relative to the control arm (dacarbazine, placebo). For those studies

	evaluating multiple doses, there was no observed dose related effect on QT interval prolongation with binimetinib administration. In conclusion, there was no evident safety signal with respect to QT prolongation with binimetinib. The binimetinib global 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 19.0 Standardized MedDRA Queries (SMQs) Torsade de pointes/QT prolongation (broad), Ventricular tachyarrhythmias (narrow) and Convulsions (narrow). There were a total of 45 cases captured with this search. There were no reported events of torsade de pointes, ventricular tachycardia, ventricular fibrillation or ventricular flutter. The majority of the cases (n=35) were due to reported events of seizure (n=25) and syncope (n=10). Of the cases of seizure, the largest number of cases (n=19) were associated with documented brain metastases associated with progression of disease. In addition, there were 2 cases assessed as related to progression of disease, 1 due to Posterior Reversible Encephalopathy Syndrome (PRES), 1 due to microangiopathic encephalopathy and 1 due to sepsis. In addition, there was one patient who experienced a seizure in the setting of gastrointestinal hemorrhage and multi-organ failure while receiving binimetinib in combination with encorafenib. This patient did expire due to the multi-organ failure. The investigator assessed this event as not related to the study drugs. Of the cases of syncope, 6 had clearly identified explanations or alternative causes (dehydration with hypotension, anemia with hypotension, vestibular neuronitis, excessive exercise with dehydration, progression of disease with cervical lymphadenopathy which the investigator associated with the syncope episode, and gastrointestinal bleeding). Furthermore, 2 of these cases had specific mention of no ECG findings and a negative cardiac evaluation. There was one syncopal event in a patient receiving binimetinib and encorafenib which was diagnosed as “vasovagal” but the investigator could not rule out that it was due to study drugs. There was a cardiology consultation with an assessment that the event was not cardiogenic. The investigator had noted a possibility of disease progression as an alternative cause. There was one syncopal event in a patient participating in a hepatic impairment study and receiving binimetinib. Although a cardiogenic origin for the event was considered, there was also an observation that the patient was alcohol intoxicated. There were two syncopal events for which there was limited information, no clear alternative causality, but the investigator assessed both cases as not related to study drug(s). One case in a patient who received single-agent binimetinib was evaluated and found to have no cardiac abnormalities. The other case occurred in a patient receiving binimetinib in combination wi
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	encorafenib with reported recurrent fainting episodes, but very limited information. The were 8 cases of cardio-pulmonary arrest captured in this search. Of these, 6 were reported with clear alternative causality of progression of disease, fentanyl overdose and heart failure. There was one case of cardio- respiratory arrest in a patient receiving binimetinib in combination with encorafenib and for which there was an important finding of pericarditis. The investigator had assessed this event of cardio-respiratory arrest as related to study drugs. There was one additional case of sudden death in a patient receiving binimetinib in combination with FOLFOX and for which there was very limited information. The investigator assessed this event as not related to study drugs, but likely related to an acute cardiac event or a pulmonary embolism. Finally, there were 2 cases of QT prolongation reported from this search. One case involved a patient receiving binimetinib as a single agent and who was found to have QT prolongation on an ECG examination associated with a Grade 2 increase in CK, but was otherwise asymptomatic. This patient was also found to have a mild increase in Troponin T and NT-proBNP. The binimetinib treatment was interrupted and the events resolved. The investigator assessed the events as related to binimetinib. The other case involved a patient receiving binimetinib in combination with erlotinib. On Day 15 of Cycle 1, a scheduled ECG found a Grade 3 QTc of 516msec with repeat finding of 523msec. The event was assessed as a dose limiting toxicity in this study and related to binimetinib. There were no reported symptoms or other findings. Binimetinib was discontinued and one week later a repeat ECG reported an improvement to Grade 1 QTc prolongation. It was also noted at this time that the patient had progressive disease with brain metastases. The outcome of the QTc prolongation was not reported. It is not clear whether or not the progression of disease had an impact on the findings of QTc prolongation. In a summary analysis of these reports from the global safety database search, aside from the observation of two events of prolonged QTc which were not associated with symptoms or complications and for which a relationship to binimetinib is not clear, there were no other events of high grade arrhythmias, seizures, syncope or cardiac arrest/sudden death which suggest an association with QT prolongation. There are clear alternative explanations for the vast majority of these events, as well as the potential of comorbidities and concomitant medications that may explain the finding.
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/s/

JIANG LIU
12/20/2016

YOUWEI N BI
12/20/2016

MOH JEE NG
12/20/2016

QIANYU DANG
12/20/2016

MICHAEL Y LI
12/20/2016

CHRISTINE E GARNETT
12/20/2016

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YOUWEI N BI
02/07/2018

JIANG LIU
02/07/2018

MOH JEE NG
02/07/2018

QIANYU DANG
02/13/2018

MICHAEL Y LI
02/13/2018

CHRISTINE E GARNETT
02/13/2018

Ophthalmology Consult Review of NDA 210498

Submission Date: June 30, 2017
Consult Request Date: November 6, 2017
Review completed: January 15, 2018

Name: binimetinib/encorafenib

Applicant: Array BioPharma, Inc.

Consult Request: DOP 2 requests an Ophthalmology consult reviewer to review the risks of renal vein occlusion and retinal pigment epithelium (RPE) associated with binimetinib in combination with encorafenib for the proposed indication: “MEKTOVI is a kinase inhibitor indicated, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test.” A previous consult review was provided under the binimetinib monotherapy application (b) (4) which was withdrawn on (b) (4). We would like to have the reviewer review the combination and identify any ophthalmology risks that may be associated with the drug.

Labeling meeting for Section 6 of PI: Wednesday, January 31, 2018; Invitations sent 11/6/17
Labeling meeting for Section 5 of PI: Thursday, February 1, 2018; Invitations sent 11/6/17
PDUFA GOAL: Saturday, June 30, 2018 (Actual Target Date: Friday, June 29, 2018)

Reviewer's Comment: *Comments are limited to areas of ophthalmic concern.*

Integrated Summary of Safety Encorafenib (LGX818) and Binimetinib (MEK162)

Ocular events included AEs reported under the 3 separate AESI groupings of retinopathy excluding RVO (retinal related events), RVO (vascular eye events) and uveitis-type events. ... The monitoring of ophthalmic events was done by the Investigator and by an ophthalmologist. For each study in the safety analysis, ophthalmic examinations included the assessments shown in Table 2-19. Across all studies in the Broad Safety Set, the full ophthalmic examination included slit lamp examination, best corrected visual acuity for distance testing, intraocular pressure (IOP) and dilated funduscopy with attention to retinal abnormalities. Additionally, OCT and/or FA were recommended/mandated for patients with clinical suspicion of retinal abnormalities. In addition, some studies included other assessments as indicated.

Ophthalmic Assessments for All Studies in the Safety Analysis

	CMEK162 B2301	CLGX818 X2109	CMEK162 X2110	CLGX818 X2102 ^a	CLGX818 X2101 ^b	CMEK162 A2301	CMEK162 X2201	CLGX818 AUS03 ^c	ARRAY- 162-311
Slit-lamp examination	X	X	X	X	X	X	X	X	X
Visual acuity	X	X	X	X	X	X	X	X	X
IOP	X	X	X	X	X	X	X	X	X
Fundoscopy	X	X	X	X	X	X	X	X	X
OCT			X	X ^d		X ^e			
Visual Field testing		X	X	X	X		X	X	X
Upon Retinal Abnormalities									
Fluorescein angiography (for vascular abnormalities)	X ^f	X	X	X	X	X	X	X	X
OCT (for non-vascular abnormalities)	X ^f	X		X ^g	X	X	X	X	X
Color fundus photography									X
ERG			X	X ^d			X (optional)		

Abbreviations: ERG = electroretinography; IOP = intraocular pressure; OCT = optical coherence tomography

^a In the original protocol (V0), the specified ophthalmologic evaluations were performed only in patients enrolled in the combination treatment arms with binimetinib during Part 2. Starting with protocol V3, the specified ophthalmologic evaluations were implemented in the entire study population.

^b Ophthalmological evaluations were added with protocol V8.

^c Ophthalmological evaluations were added with protocol V1.

^d For patients enrolled in the combination treatment arms with binimetinib during Part 2.

^e OCT was added as a routine assessment for only newly enrolled patients randomized to the binimetinib treatment arm starting with protocol V4.

^f Additional evaluations to be performed upon observation of retinal abnormalities were added with protocol V1.

^g For patients enrolled in Part 1.

Retinopathy Excluding Retinal Vein Occlusion

Serous retinopathy is a well-known MEK inhibitor-associated class effect ([Mekinist® \[trametinib\] prescribing information](#); [Cotellic® \[cobimetinib\] prescribing information](#)) and has been observed with binimetinib treatment. MEK inhibitor-associated retinopathy has been described in the literature using a number of various terms including serous retinopathy, central serous retinopathy, serous retinal detachments, retinopathy and RPED. Clinical findings usually are characterized by serous retinal detachments and may be accompanied by the presence of subretinal fluid and disarrangement of the outer retinal layers. Symptomatic findings vary widely and may include early onset, often bilateral, mild transient visual disturbances which can include blurred vision, altered color perception, shadows, light sensitivity, metamorphopsia and glare ([Stjepanovic et al 2016](#)).

In Study CMEK162B2301, Grade 1 retinal AEs were defined as asymptomatic (but with findings of serous retinal detachment in OCT, fundoscopy or biomicroscopy) and the recommendation for the Combo 450, Combo 300 and encorafenib arms were to maintain the dose levels of both encorafenib and binimetinib with repeat ophthalmic monitoring and OCT.

In Study CMEK162B2301, Grade 2 retinal AEs were defined as symptomatic with moderate decrease in VA (20/40 or better) with limiting instrumental activities of daily living. Protocol recommendations for Grade 2 events in the Combo 450, Combo 300 and encorafenib arms were to interrupt encorafenib and binimetinib dosing and repeat ophthalmic monitoring including VA assessment and OCT within 10 days. If the event resolved to baseline or Grade ≤ 1 , encorafenib and binimetinib were to be resumed at the same dose levels with continued ophthalmic monitoring including VA assessment and OCT at protocol-defined visits. For Grade 2 events which did not resolve to baseline or Grade ≤ 1 , encorafenib and binimetinib were to be resumed at a reduced dose level with continued ophthalmic monitoring including VA assessment and OCT at protocol defined visits.

In Study CMEK162B2301, Grade 3 retinal AEs were defined as symptomatic with marked decrease in VA ($> 20/40$) with limiting self-care activities of daily living. In the event a patient experienced a Grade 3 retinal event in the Combo 450, Combo 300 or encorafenib arms, encorafenib and binimetinib were to be interrupted and ophthalmic monitoring was to be repeated, including VA assessment and OCT performed within 10 days. If the event resolved to baseline or Grade ≤ 2 , encorafenib and binimetinib were to be resumed at a reduced dose level with continued ophthalmic monitoring including VA assessment and OCT at each visit. If the Grade 3 retinal event was not resolved to baseline or Grade ≤ 2 , per the protocols, encorafenib and binimetinib treatments were to be permanently discontinued.

In Study CMEK162B2301, Grade 4 retinal AEs were defined as blindness (20/200 or worse) in the affected eye and, per the protocols, encorafenib and binimetinib treatments were to be permanently discontinued.

Frequency

In Study CMEK162B2301 Part 1, retinopathy excluding RVO events were reported in a higher percentage of patients in the Combo 450 arm as compared with the encorafenib Part 1 and vemurafenib arms (48.4% Combo 450 arm, 13.5% encorafenib Part 1 arm, 12.4% vemurafenib arm).

Ophthalmology Consult Encorafenib (LGX818)/Binimetinib (MEK162) NDA 210-498

Retinopathy Excluding Retinal Vein Occlusion Events, Regardless of Study Drug Relationship, by Preferred Term and Treatment – ($\geq 2.0\%$ in CMEK162B2301 Part 1 Combo 450 Arm) (Broad Safety Set, Part 1)

Melanoma

Study CMEK162B2301 Part 1

Preferred Term	Binimetinib 45 mg BID N=427 n (%)	Encorafenib 300 mg QD N=217 n (%)	Combo pooled doses N=433 n (%)	Combo 450 mg QD N=274 n (%)	Combo 450 mg QD N=192 n (%)	Encorafenib 300 mg QD N=192 n (%)	Vemurafenib N=186 n (%)
Total	189 (44.3)	27 (12.4)	232 (53.6)	144 (52.6)	93 (48.4)	26 (13.5)	23 (12.4)
Vision blurred	28 (6.6)	5 (2.3)	67 (15.5)	42 (15.3)	30 (15.6)	4 (2.1)	4 (2.2)
Retinal detachment	44 (10.3)	1 (0.5)	21 (4.8)	18 (6.6)	15 (7.8)	1 (0.5)	1 (0.5)
Visual field defect	13 (3.0)	2 (0.9)	24 (5.5)	18 (6.6)	14 (7.3)	2 (1.0)	3 (1.6)
Macular oedema	19 (4.4)	0	20 (4.6)	14 (5.1)	11 (5.7)	0	1 (0.5)
Photophobia	3 (0.7)	3 (1.4)	14 (3.2)	8 (2.9)	7 (3.6)	3 (1.6)	3 (1.6)
Subretinal fluid	24 (5.6)	0	36 (8.3)	17 (6.2)	7 (3.6)	0	0
Eye disorder	5 (1.2)	1 (0.5)	8 (1.8)	6 (2.2)	6 (3.1)	1 (0.5)	0
Visual impairment	25 (5.9)	7 (3.2)	23 (5.3)	11 (4.0)	6 (3.1)	7 (3.6)	2 (1.1)
Chorioretinopathy	13 (3.0)	0	16 (3.7)	9 (3.3)	5 (2.6)	0	0
Retinal disorder	14 (3.3)	0	5 (1.2)	5 (1.8)	4 (2.1)	0	0
Retinopathy	22 (5.2)	1 (0.5)	46 (10.6)	26 (9.5)	4 (2.1)	1 (0.5)	0
Visual acuity reduced	9 (2.1)	1 (0.5)	8 (1.8)	5 (1.8)	4 (2.1)	1 (0.5)	3 (1.6)

Month 4 Follow-up ADR: Serous Retinopathy (CMEK162B2301 Part 1, Combo 450 Arm)

	Total	Led to Treatment Discontinuation	Led to Dose Interruption or Adjustment	Median Time To First Onset (Any Grade)
Initial	19.8%	0%	5.7%	38 days
4-Mo SU	19.8%	0%	5.7%	38 days

Retinal Vein Occlusions

Retinal vein occlusion has been observed with MEK-inhibitor treatment ([Mekinist \[trametinib\] prescribing information](#); [Cotellic® \[cobimetinib\] prescribing information](#)), including binimetinib.

Frequency

In Study CMEK162B2301 Part 1, no RVO events were reported in any patients in the Combo 450 or vemurafenib arms. One patient (0.5%; [CMEK162B2301 Patient 4027-024](#)) in the encorafenib Part 1 arm experienced an RVO event. There were no events of RVO in the 2 Combo-treated pooled populations and no additional events were reported in the Encorafenib 300 mg population.

In the Binimetinib 45 mg population, there were 9 patients (6 patients in Study CMEK162A2301 and 3 patients in Study CMEK162X2201) who experienced events in the RVO grouping, all under the PT of RVO, with an incidence of ($\leq$ 1.2% of patients).

Retinal Vein Occlusion Events, Regardless of Study Drug Relationship, by Preferred Term and Treatment

	Melanoma				Study CMEK162B2301 Part 1		
	Binimetinib 45 mg BID	Encorafenib 300 mg QD	Combo pooled	Combo 450 mg QD	Combo 450 mg QD	Encorafenib 300 mg QD	Vemurafenib
	N=427	N=217	N=433	N=274	N=192	N=192	N=186
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	9 (2.1)	1 (0.5)	0	0	0	1 (0.5)	0
Retinal artery	0	1 (0.5)	0	0	0	1 (0.5)	0
Retinal vein	9 (2.1)	0	0	0	0	0	0

Abbreviations: BID = twice daily; Combo = encorafenib plus binimetinib; mg = milligram(s); QD = once daily

A patient with multiple adverse events within a preferred term is counted only once in that preferred term. Preferred terms are sorted in descending frequency of the Combo 450 mg column of Study CMEK162B2301. Source: [ISS Table 2.1.8.2](#)

Reviewer's Comment: *The 4-month safety update included no additional reports of retinal vein occlusion.*

Uveitis-type Events

Uveitis has been observed with BRAF-inhibitor treatment (Tafinlar® [dabrafenib] [prescribing information](#); Zelboraf® [vemurafenib] [prescribing information](#)), including encorafenib.

Uveitis describes intraocular inflammation involving the uvea tract (iris, ciliary body and choroid). It can produce swelling and destruction of eye tissues and be associated with slightly reduced vision or lead to severe vision loss.

Frequency

In Study CMEK162B2301 Part 1, uveitis-type events were reported in a similar percentage of patients in the Combo 450 and vemurafenib arms and in a lower percentage in the encorafenib Part 1 arm (3.6% Combo 450 arm, 0.5% encorafenib Part 1 arm, 3.8% vemurafenib arm).

Comparison of Combo 450 to Combo 300

Overall in Study CMEK162B2301, uveitis-type events were similarly reported in patients in the Combo 450 arm of Study CMEK162B2301 Part 1 (3.6% [0.5% Grade 3/4]) as compared with the Combo 300 arm of Study CMEK162B2301 Part 2 (3.9% [1.6% Grade 3/4]).

Uveitis-type Events, Regardless of Study Drug Relationship, by Preferred Term and Treatment

Melanoma				Study CMEK162B2301 Part 1			
	Binimetinib 45 mg BID	Encorafenib 300 mg QD	Combo pooled	Combo 450 mg QD	Combo 450 mg QD	Encorafenib 300 mg QD	Vemurafenib
	N=427	N=217	N=433	N=274	N=192	N=192	N=186
Preferred	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	1 (0.2)	1 (0.5)	16 (3.7)	8 (2.9)	7 (3.6)	1 (0.5)	7 (3.8)
Uveitis	1 (0.2)	0	7 (1.6)	5 (1.8)	5 (2.6)	0	3 (1.6)
Iridocyclitis	0	1 (0.5)	8 (1.8)	5 (1.8)	4 (2.1)	1 (0.5)	3 (1.6)
Iritis	0	0	4 (0.9)	1 (0.4)	1 (0.5)	0	1 (0.5)
Autoimmune	0	0	0	0	0	0	1 (0.5)

Abbreviations: BID = twice daily; Combo = encorafenib plus binimetinib; mg = milligram(s); QD = once daily. A patient with multiple adverse events within a preferred term is counted only once in that preferred term. Preferred terms are sorted in descending frequency of the Combo 450 mg column of Study CMEK162B2301. Source: [ISS Table 2.1.10.2](#)

Month 4 Follow-up ADR: Uveitis (CMEK162B2301 Part 1, Combo 450 Arm)

	Total	Led to Treatment Discontinuation	Led to Dose Interruption or Adjustment	Median Time To First Onset (Any Grade)
Initial	3.6%	0%	3.1%	not reported (too few patients)
4-Mo SU	4.2%	0%	3.1%	153 days

Reviewers Comment:

Patients treated with the combination of encorafenib and binimetinib have ophthalmologic adverse reactions consistent with the adverse reactions seen in the representative classes of products.

These adverse reactions included bilateral, multifocal retinal pigment epithelial detachments (RPED), retinal vein occlusions (RVO) and uveitis. RVO events have routinely led to discontinuation. Uveitis may be treated with topical corticosteroids. RPED events will sometimes resolve without dose modification. If the RPED is not demonstrated to be improving within 3 weeks, it is recommended that the product be reduced or stopped.

From an ophthalmic prospective, there is no objection to the approval of NDA 210498, with Warning/Precautions, Adverse Reaction listings, and Dose recommendations similar to those related to RPE detachments and RVO previously recommended for other MEK inhibitors, along with Uveitis Warning/Precautions and Adverse Reactions.

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/s/

WILEY A CHAMBERS
01/16/2018

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}

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/s/

NAVID N HOMAYOUNI
12/28/2017

SUSAN D THOMPSON
12/28/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

FROM: Steven Lemery, M.D., M.H.S.
Associate Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Review Designation Memo for NDA 210498

TO: NDA 210498

The review status of this file submitted as an original NDA is designated to be:

Standard (PDUFA V - 10 Months)

In the original NDA submission, Array BioPharma Inc., requested priority review designation for the following indication: *Binimetinib is indicated, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test.*

Qualifying Criteria for Priority Review Designation

1. Serious Condition:

I agree that unresectable or metastatic melanoma (with a BRAF V600E or V600K mutation) is a life threatening disease and therefore qualifies as a serious condition.

2. Demonstrating the Potential to Be a Significant Improvement in Safety or Effectiveness:

FDA's May 2014 Expedited Programs Guidance states that *generally, if there is an available therapy (see section III.B.), sponsors should compare their investigational drug to the available therapy in clinical testing with an attempt to show superiority relating to either safety or effectiveness. Alternatively, sponsors could show the drug's ability to effectively treat patients who are unable to tolerate, or whose disease failed to respond*

to, available therapy or show that the drug can be used effectively with other critical agents that cannot be combined with available therapy.

To date, two RAF and MEK combinations have received regular approval for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test: dabrafenib with trametinib *and* vemurafenib with cobimetinib.

In the request for priority review, Array did not provide arguments that the combination binimetinib and encorafenib provides for a significant improvement in effectiveness over available therapy. Array argued that the binimetinib and encorafenib combination induces less pyrexia than dabrafenib plus trametinib (57%, USPI) and that binimetinib and encorafenib induces less photosensitivity than cobimetinib and vemurafenib (47%, USPI).

I do not agree that these arguments are sufficient to grant priority review designation. First, in regards to photosensitivity with cobimetinib and vemurafenib, although photosensitivity occurred in 47% of patients, only 4% of patients experienced Grade 3 photosensitivity and photosensitivity was generally managed by sun avoidance, sunscreen, etc. Furthermore, photosensitivity was not listed as one of the common adverse events leading to dose modifications of cobimetinib in the cobimetinib product labeling.

Although fever occurred in 57% (17% severe) of patients receiving dabrafenib in combination with trametinib, median duration of fever was three days and only 1.4% of patients required treatment discontinuation of trametinib (1.9% for dabrafenib) due to fever. Dose reductions due to fever occurred in 26% of patients for dabrafenib and 2.9% for trametinib indicating that this adverse event was generally managed through dose modification and anti-pyrexia drugs.

Importantly, binimetinib and encorafenib share many of the other toxicities caused by RAF/MEK inhibition (e.g., skin neoplasia with RAF inhibition and left ventricular dysfunction/ocular toxicities).

Based on these considerations, Array did not provide a sufficient argument that binimetinib or encorafenib can effectively treat patients who are unable to tolerate either of the other two RAF/MEK combinations (or single agents if applicable). Array did not conduct a comparative trial and did not enroll patients who were intolerant of other RAF/MEK inhibitors in Study CMEK162A2301. Additionally, Array did not address the availability of ipilimumab or pembrolizumab which are approved for patients with untreated melanoma, regardless of BRAF mutation status (nivolumab would not qualify as available therapy in this population because nivolumab, as a single agent, has received accelerated approval for patients with BRAF V600 mutation-positive unresectable or metastatic melanoma).

This decision is consistent with the standard review designation granted to dabrafenib for the initial NDA that was approved on May 29, 2013 (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/202806Orig1s000Admincorres.pdf). This was granted in the setting of availability of vemurafenib and different incidence rates of pyrexia/photosensitivity between the two drugs.

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/s/

STEVEN J LEMERY
08/22/2017