26 July 2018
EMA/CHMP/554701/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mektovi

International non-proprietary name: binimetinib

Procedure No. EMEA/H/C/004579/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

ADME	Absorption, distribution metabolism and excretion
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC_{0-12}	Area under the concentration-time curve from time 0 to 12 hours
$AUC_{tau,ss}$	Area under the concentration-time curve from time 0 to the end of the dosing interval tau at steady state
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BID	Twice-daily
BIRC	Blinded independent review committee
BRAF	V-raf murine sarcoma viral oncogene homolog B1
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence intervals
CK	Creatine kinase
CL/F	Apparent total clearance following oral administration
Cmax	Maximum observed plasma concentration
Cmax,ss	Maximum observed plasma concentration at steady state
Cmin,ss	Minimum observed plasma concentration at steady state
CrCL	Calculated creatinine clearance
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Human cytotoxic T-lymphocyte antigen-4
CYP	Cytochrome P450
DCR	Disease control rate

DOR	Duration of response
DRESS	Drug reaction with eosinophilia and systemic symptoms
DSC	Differential scanning calorimetry
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EU	European Union
FAS	Full Analysis Set
GC	Gas chromatography
HPLC	High performance liquid chromatography
HR	Hazard ratio
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INR	International Normalized Ratio
IPC	In-process control
IOP	Intraocular pressure
IR	Infrared absorption spectrophotometry
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISE	Integrated Summary of Effectiveness
ISS	Integrated Summary of Safety
ITT	Intention-to-Treat
IV	Intravenous(ly)
KF	Karl-Fisher titration
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma viral oncogene homolog
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MAA	Marketing Authorisation Application
MAP	Mitogen-activated protein

MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase
MEK162	Binimetinib
MEK162-4	Methyl 2,4-diamino-3-fluoro-5-nitrobenzoate
MUGA	Multi-gated acquisition
MS	Mass spectrometry
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not estimable
NLT	Not less than
NMR	Nuclear magnetic resonance
NRAS	Neuroblastoma RAS viral (v-ras) oncogene homolog
OCT	Optical coherence tomography
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein 1
pERK	Phosphorylated extracellular signal-regulated kinase
PFS	Progression-free survival
P-gp	Phosphorylated glycoprotein
PIP	Paediatric investigational plan
PK	Pharmacokinetics
PRO	Patient-Reported Outcome
PT	Preferred term
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	Recommended Phase 2 dose
RPED	Retinal pigment epithelium detachment
RVO	Retinal vein occlusion
SAE	Serious adverse event
t1/2	Apparent terminal half-life
TLC	Thin layer chromatography

Tmax	Time to maximum observed plasma concentration
TNFα	Tumours necrosis factor alpha
TTR	Time to response
UGT	Uridine glucuronosyltransferase
UHPLC	Ultra-performance liquid chromatography
ULN	Upper limit of normal
UV	Ultra violet spectroscopy
VTE	Venous thromboembolism
Vz/F	Volume of central distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pierre Fabre Medicament submitted on 28 July 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Mektovi, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 July 2016.

The applicant applied for the following indication: Binimetinib in combination with encorafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see section 4.4).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

This application is submitted, in accordance with Article 82.1 of Regulation (EC) No 726/2004, as a multiple of Balimek (EMEA/H/C/004052), which at the time of filing of this application was under initial assessment.

Of note, the application for Balimek (EMEA/H/C/004052) was withdrawn by the applicant on 4 January 2018. As a consequence, the present application does not fall under Article 82.1 of Regulation (EC) No 726/2004 anymore.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P0051/2016 on the agreement of a paediatric investigation plan (PIP) and CW/1/2011 on the granting of a class waiver.

At the time of submission of the application, the PIP P0051/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance binimetinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a

medicinal product previously authorised within the European Union.

Scientific advice

The applicant did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Nithyanandan Nagercoil Co-Rapporteur: Harald Enzmann

The application was received by the EMA on	28 July 2017
The procedure started on	17 August 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	3 November 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	30 October 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	17 November 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 December 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	28 March 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	4 May 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 May 2018
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on	31 May 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 June 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	11 July 2018
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	20 July 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Mektovi on	26 July 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Cutaneous melanoma, which arises from the oncogenic transformation of melanocytes that reside in the epidermal layer of the skin, is the most lethal form of skin cancer, due to its propensity to metastasise to vital organs, including the brain, lungs, liver and other visceral organs[1]. Malignant melanoma is the 19th most common cancer worldwide, with around 232,000 new cases (2% of the total) diagnosed in 2012[2],[3]. Malignant melanoma is the ninth most common cancer in Europe, with 123,135 new cases (3% of the total) diagnosed in 2012. The European incidence of malignant melanoma varies from 3 to 5/100 000/year in Mediterranean countries to 12–25 (and rising) in Nordic countries. The most common phenotypic risk factor for developing cutaneous melanoma is having fair skin that tends to burn in the sun. Genetic risk factors also include inheriting melanocortin-1 receptor variant as well as the presence of high numbers of common naevi and those with large congenital naevi, multiple and/or atypical naevi (dysplastic naevi) are at a greater risk to developing cutaneous melanoma. The most important external risk factor is prolonged exposure to UV irradiation, particularly intermittent sun exposure.

2.1.2. Biologic features

There are four main subtypes of cutaneous melanomas: superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, acral lentiginous melanoma. These can be clinically and histologically defined based on overall appearance, location and histologic features of the melanocytes. Approximately 50% of patients with metastatic melanoma have mutations in *BRAF*, and over 95% of these are in *BRAF* exon 15 at V600. The most common V600 mutations are V600E and V600K accounting for 66-91% and 7-30% of all *BRAF* V600 mutations, respectively[4],[5],[6],[7],[8]. These mutations constitutively activate BRAF protein and downstream signal transduction in the RAF/MEK/ERK pathway (MAPK pathway), which signals for cancer cell proliferation and survival.

2.1.3. Clinical presentation, diagnosis and stage / prognosis

Over 90% of melanomas are diagnosed as primary tumours without any evidence of metastasis. The tumour-specific 10-year survival for such tumours is 75%-85%, with 10–20% of cases becoming metastatic and eventually fatal[9], . However, the survival rate of unresectable or metastatic melanoma decreases sharply; the 5-year survival rate is 17% and, if left untreated, the median survival is 6-9

[1] Garbe C., Peris K., Hauschild A. et al. Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline - Update 2016. Eur J Cancer. 2016 Aug; 63: 201-17
[2] Ferlay J., Steliarova-Foucher E., Lortet-Tieulent J. et al Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013 Apr;49(6):1374-403.
[3] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar 1;136(5):E359-86
[4] Davies H, Bignell GR, Cox C et al. Mutations of the BRAF gene in human cancer. Nature 2002;417(6892):949-54.
[5] Cheng S, Chu P, Hinshaw M et al. Frequency of mutations associated with targeted therapy in malignant melanoma patient. J Clin Oncol 2011; 29(suppl; abstr 8597)
[6] Colombino M., Capone M., Lissia A. et al BRAF/NRAS mutation frequencies among primary tumors and metastases in patients with melanoma. J. Clin. Oncol., 2012; 30(20): 2522-9
[7] Jakob J.A., Bassett R.L. Jr., Ng CS et al. NRAS mutation status is an independent prognostic factor in metastatic melanoma. Cancer 2012;118(16):4014-23
[8] Greaves WO, Verma S, Patel KP et al. Frequency and spectrum of BRAF mutations in a retrospective, single-institution study of 1112 cases of melanoma. J Mol Diagn 2013;15(2): 220-6
[9] Zbytek B, Carlson J.A., Granese J, Ross J, et al. Current concepts of metastasis in melanoma Expert review of dermatology. 2008;3(5):569-85

months. The clinical presentation of cutaneous melanoma varies depending on the subtype but the typical features relate to asymmetry of the lesion, irregular borders, colour and diameter of the lesions. The most important prognostic factors in metastatic melanoma are the site(s) of metastases (presence of visceral metastases) and the presence of elevated serum lactate dehydrogenase (LDH). Prognosis is particularly poor in patients with American Joint Committee on Cancer (AJCC) stage IV M1c melanoma, defined as disease that has metastasised to visceral organs (other than the lungs) and LDH is normal or with elevated LDH and any distant metastases, with an estimated 1-year survival rate of 33%[10].

Table 1: AJCC staging of melanoma (7th edition)

ANATOMIC STAGE/PROGNOSTIC GROUPS							
Clinical Staging[3]				Pathologic Staging[4]			
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	IA	T1a	N0	M0
Stage IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
Stage IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
Stage IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
Stage IIC	T4b	N0	M0	IIC	T4b	N0	M0
Stage III	Any T	≥ N1	M0	IIIA	T1-4a	N1a	M0
					T1-4a	N2a	M0
				IIIB	T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
Stage IV	Any T	Any N	M1	IV	Any T	Any N	M1

Notes

[1] Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed).

[2] Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

[3] Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

[4] Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 or Stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

2.1.4. Management

The current treatment options for metastatic melanoma include 2 classes of agents, immune checkpoint inhibitors and kinase inhibitors targeting the MAPK pathway in patients with *BRAF* mutations. BRAF and its downstream target, MEK, are kinases in the MAPK pathway, and play an important role in cell proliferation[11]. These new therapies have been shown to prolong survival in

[10] Dickson PV and Gershenwald JE. Staging and prognosis of cutaneous melanoma. Surg Oncol Clin N Am. 2011 Jan;20 (1):1-17

[11] Peyssonnaux C, Eychène A. The Raf/MEK/ERK pathway: new concepts of activation. Biol Cell. 2001;93(1–2):53–62

recent Phase 3 clinical trials[12], [13], [14], [15], [16], [17], with the BRAF/MEK combinations vemurafenib/cobimetinib and dabrafenib/trametinib increasing the median progression-free survival (PFS) to approximately 12 months and the median overall survival (OS) to 22-26 months in metastatic melanoma with a *BRAF* mutation,.

Vemurafenib single-agent was the first BRAF inhibitor to be approved for patients with advanced unresectable or metastatic *BRAF*-mutant melanoma, followed by dabrafenib single-agent. In the pivotal Phase 3 studies, the median PFS was 5.3 months with vemurafenib and 1.6 months with dacarbazine[18] while median PFS was 5.1 months for dabrafenib and 2.7 months for dacarbazine[19]. The duration of response (DOR) for single agent BRAF inhibition is often short lived, with resistance developing within approximately 6 months, [20], . To delay resistance to BRAF inhibition, the combination of BRAF- and a MEK1/2-inhibitors showed prolonged durationof the response in patients with advanced *BRAF*-mutant melanoma[21], [22], . In addition, the combination of a MEK inhibitor and a BRAF inhibitor appears to result in improved tolerability compared with either agent alone, , , , . Based on these data, the BRAF/MEK inhibitors have been the standard of care for patients with previously untreated unresectable or metastatic *BRAF* V600E or V600K mutation-positive melanoma. Recent European consensus-based interdisciplinary guidelines recommend the use of the BRAF/MEK inhibitor combinations dabrafenib/trametinib or vemurafenib/cobimetinib for the treatment of *BRAF*-mutated unresectable or metastatic melanoma patients, where targeted therapy is indicated and the combination has overtaken BRAF monotherapies (e.g. vemurafenib monotherapy) as the current standard of care.

About the product

Binimetinib is an ATP-uncompetitive, reversible inhibitor of the kinase activity of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. In cell free system, binimetinib inhibits MEK1 and MEK2 with the half maximal inhibitory concentration (IC_{50})'s in the 12-46 nM. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. In melanoma and other cancers, this pathway is often activated by mutated forms of BRAF which activates MEK. Binimetinib inhibits activation of MEK by BRAF and inhibits MEK kinase

[12] Chapman P.B., Hauschild A., Robert C. et al Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N. Engl. J. Med., 2011; 364(26): 2507-16
[13] Hodi F.S. O'Day S.J. McDermott D.F. et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010 Aug 19;363(8):711-23
[14] Larkin J., Ascierto P.A., Dréno B. et al Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N. Engl. J. Med., 2014; 371(20): 1867-76
[15] Robert C., Karaszewska B, Schachter J et al Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib. N. Engl. J. Med., 2015a; 372: 30-9
[16] Robert C., Long G.V., Brady B. et al. Two year estimate of overall survival in COMBI-v, a randomized, open-label, phase III study
comparing the combination of dabrafenib (D) and trametinib (T) with vemurafenib (Vem) as firstline therapy in patients (pts) with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma. Eur J Cancer 2015b 51 sup3: S-663
[17] Ascierto P.A., McArthur G.A., Dréno B. et al. Cobimetinib combined with vemurafenib in advanced BRAFV600-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol. 2016 ;17(9):1248-60
[18] Chapman P.B., Hauschild A., Robert C. et al Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N. Engl. J. Med., 2011; 364(26): 2507-16
[19] Hauschild A., Grob J.J., Demidov L.V. et al Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet, 2012(9839); 380: 358-65
[20] McArthur GA, Chapman PB, Robert C et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol 2014;15(3):323-32
[21] Flaherty K.T., Robert C., Hersey P. et al Improved survival with MEK inhibition in BRAF-mutated melanoma. N. Engl. J. Med., 2012; 367(2):107-14
[22] Long GV, Stroyakovskiy D, Gogas H et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 2014; 371(20):1877-88

activity. Binimetinib inhibits growth of BRAF V600 mutant melanoma cell lines and demonstrates anti-tumour effects in BRAF V600 mutant melanoma animal models.

Combination with encorafenib

Binimetinib and encorafenib (a BRAF inhibitor, see section 5.1 of encorafenib SmPC) both inhibit the MAPK pathway resulting in higher anti-tumour activity.

Additionally, the combination of encorafenib and binimetinib prevented the emergence of treatment resistance in BRAF V600E mutant human melanoma xenografts *in vivo.*

The applicant applied for the following indication:

"Binimetinib is indicated for use in combination with encorafenib for the treatment of adult patients with unresectable or metastatic melanoma, with BRAF V600 mutation."

The agreed final indication is as follows:

"Binimetinib in combination with encorafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see sections 4.4 and 5.1)."

Binimetinib will be supplied as 15 mg film-coated tablets for oral administration. Each film-coated tablet contains 15 mg of binimetinib. Each film coated tablet contains 133.5 mg of lactose monohydrate.

The recommended dose of binimetinib is 45 mg (three 15 mg tablets) twice daily, corresponding to a total daily dose of 90 mg approximately 12 hours apart.

Binimetinib treatment in combination with encorafenib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products.

Method of administration

Mektovi is for oral use.

The tablets are to be swallowed whole with water. They may be taken with or without food. In case of vomiting after administration of binimetinib, the patient should not re-take the dose and should take the next scheduled dose.

Duration of treatment
Treatment should continue until the patient no longer derives benefit or the development of unacceptable toxicity.

Missed doses
If a dose of binimetinib is missed, it should not be taken if it is less than 6 hours until the next dose is due.

Type of Application and aspects on development

Scientific advice was given by 2 national European (EU) Agencies (Medical Products Agency [MPA] and Medicines Evaluation Board [MEB]) on the design of the pivotal Phase 3 study CMEK162B2301, intended to establish the safety and efficacy of binimetinib 45 mg BID in combination with encorafenib 450 mg QD vs vemurafenib 960 mg BID and encorafenib 300 mg QD monotherapies in patients with unresectable or metastatic *BRAF* V600-mutant melanoma. The choice of PFS as primary endpoint for

the study as well as the proposed central response assessment was agreed. However, the importance of presenting the overall survival data, was also highlighted. Hierarchical and event-driven statistical testing strategy was agreed in a follow-up advice meeting with the MPA.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a film-coated tablet containing 15 mg of binimetinib as active substance.

Other ingredients of the tablet core are: lactose monohydrate, cellulose microcrystalline (E460i), silica colloidal anhydrous (E551), croscarmellose sodium (E468) and magnesium stearate (E470b).

Other ingredients of film-coating of the tablet are: polyvinyl alcohol (E1203), macrogol 3350 (E1521), titanium dioxide (E171), talc (E533b), iron oxide yellow (E172), and iron oxide black (E172).

The product is available in PVC/PVDC/Alu blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of binimetinib is 5-[(4-bromo-2-fluorophenyl)amino]-4-fluoro-*N*-(2-hydroxyethoxy)-1-methyl-1*H*-benzimidazole-6-carboxamide corresponding to the molecular formula $C_{17}H_{15}BrF_2N_4O_3$. It has a relative molecular mass of 441.23g/mol and the following structure:

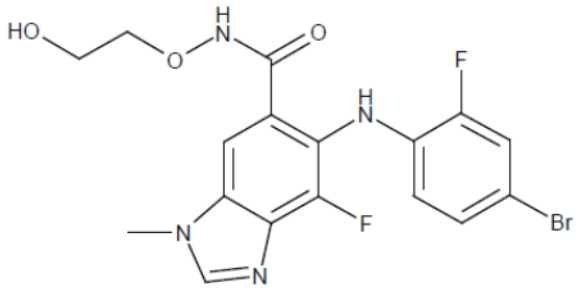


Figure 1: active substance structure

The chemical structure of binimetinib was elucidated by a combination of infrared absorption spectrophotometry (IR), ultraviolet spectroscopy (UV) in different media, proton and carbon nuclear magnetic resonance (NMR) spectroscopy, and mass spectrometry (MS).

Binimetinib is a white to slightly yellow powder. As discussed under the pharmaceutical development of the finished product, the particle size of the active substance is controlled. Binimetinib does not contain any chiral centres; hence, it is not chiral.

Manufacture, characterisation and process controls

Binimetinib is synthesised insteps using well defined starting materials with acceptable specifications. A synthesis scheme and a detailed, comprehensive synthesis description have been provided including standard quantities or molar equivalents of used raw materials, solvents and reagents as well as temperatures, pressure/vacuum conditions, pH values and times.

IPCs and critical process steps are indicated in the narrative description.
Adequate IPCs are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. Mutagenic impurities are controlled in an intermediate in line with ICH M7 guidance.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced in the manufacturing process have been presented in sufficient detail, justified and supported with bridging studies when needed.

The active substance is packaged in double polyethylene (PE) bags which comply with the EC directive 2002/72/EC and EC 10/2011 as amended. The bags are placed into 120 L metallic drums.

Specification

The active substance specification includes tests for appearance, identification (IR), water content (by Karl-Fisher titration method (KF)), sulphated ash (Ph.Eur.), residual solvents (gas chromatography (GC)), particle size (laser diffraction), assay and related substances (ultra-performance liquid chromatography (UHPLC)) and microbiological examination (Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis data (batches manufactured at commercial scale with the proposed commercial process) of the active substance were provided. The results were within the specifications and consistent from batch to batch.

Stability

Stability data from commercial scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the marketunder long term conditions and under accelerated conditionsaccording to the ICH guidelines was provided.

The following parameters were tested: appearance, polymorphic form, assay, related substances, water content and microbial purity. The analytical methods used were the same as for release and are stability indicating

All tested parameters were within the specifications and no significant trends were observed. Photostability testing following the ICH guideline Q1B was performed on one batch.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Mektovi is an immediate release film-coated tablet for oral administration. The tablet is ovaloid biconvex (capsule shaped), yellow to dark yellow in colour, and debossed with a stylized “A” on one side and “15” on the other. The length of the film-coated tablet is approximately 12 mm. The width of the film-coated tablet is approximately 5 mm.

Mektovi is an immediate release film-coated tablet for oral administration. The development of the formulation and manufacturing process were conducted following a traditional empirical pharmaceutical development approach that targeted an immediate release oral product with complete disintegration and rapid dissolution in the stomach that would achieve acceptable bioavailability and would allow for room temperature storage.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The dissolution specification has been set according the clinical batches used which dissolution profiles have been presented. No overages are used in the manufacture of the finished product.

The primary packaging is PVC/PVDC/Alu blister. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of blending, milling, compression, film-coating and packaging. The content of active substance exceeds 2% of the finished dosage form; hence, the process is considered to be a standard manufacturing process.

Formal process validation studies for batches manufactured at the proposed commercial scale have been presented. The bulk holding time is justified based on the stability data provided. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The IPCs are adequate for this pharmaceutical form.

Product specification

The finished product release specifications shown in include appropriate tests for this kind of dosage form: appearance, identification (thin layer chromatography (TLC) and High performance liquid chromatography (HPLC)) assay and related products (UHPLC/UV), uniformity of dosage units by content uniformity (HPLC), dissolution (HPLC), water content (KF) and microbiological examination.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standard used for assay has been presented, as discussed in the active substance section.

Batch analysis results were provided for commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from batches of finished productstored under long term conditions andunder accelerated conditions according to the ICH guidelines were provided. The batches of Mektovi are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay and related products, dissolution, water content and microbial enumeration. The analytical procedures used are stability indicating. No significant changes or trends were observed under any of the storage conditions.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Data presented for tablet appearance, assay, individual and total unspecified degradation products and dissolution show no changes following exposure.

Data to demonstrate stability to temperature excursions which could be encountered during shipping or storage, i.e. refrigerated, frozen and exposed to cycles of freeze / thaw conditions were also presented. The data indicate no adverse impact on product quality from such temperature excursions.

Based on available stability data, the proposed shelf-life of 36 months without special temperature storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

All constituent parts of the formulation are of non-biological/chemical origin, with the exception of lactose monohydrate for which a suitable TSE declaration has been provided. It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Pharmacology studies were performed for the binimetinib alone as well as the combination of encorafenib with binimetinib in both *in vitro* (isolated enzyme and cell culture) and *in vivo* (mouse xenograft) model systems. Pharmacokinetic studies were conducted in mice, rats and monkeys with binimetinib administered either orally or/and intravenously. No PK, ADME or toxicology studies have been performed with the combination. The safety pharmacology and toxicology studies were performed in accordance with GLP (unless otherwise indicated).

2.3.2. Pharmacology

Primary pharmacodynamic studies

The activity of binimetinib against purified MEK1 has been evaluated using standard screening assays. Measurements of the IC50 for binimetinib at a concentration of ATP at/near its Km(app) (10 µM) yielded an average value of 12.1 ± 5.6 nM (n=4). Results of the enzymatic studies revealed that binimetinib is a weakly time-dependent, slowly reversible, allosteric inhibitor of MEK that displays uncompetitive inhibition versus ATP and non-competitive inhibition versus the substrate ERK2.

Viability and p-ERK Inhibition by binimetinib in B-Raf-Mutant Human Melanoma Cell Lines

In viability assays, binimetinib was most potent in A375 and UACC-62 cell lines (Table 2) and less sensitive in cell lines IGR-39, MDA-MB435S and RPMI-7051, both by relatively high IC50 values and by low maximal inhibition of about 50%. IGR-1, WM-115 and Colo-800 lines showed medium sensitivity in this panel. Cell lines of variable sensitivity (UACC-62, WM- 115 and Colo-800) showed signs of cell death after treatment with MEK162.

Table 2: Effect of binimetinib Single Agent on p-ERK in B-Raf-Mutant Melanoma Cell Lines

Cell Lines	Concentrations Used (nM)	p-ERK		
		Relative IC_{50} (nM)	Absolute IC_{50} (nM)	Max. Inhibition (%)
A375	0.13 - 10,000	17.1	27.4	87.4
UACC-62	0.13 - 10,000	13.1	14.4	76.1
RPMI-7951	0.13 - 10,000	57.9	125.8	73.0
Colo-800	0.13 - 10,000	5.3	7.6	97.3

B-Raf mutant melanoma cells were seeded at 15,000 cells per well in triplicate black 96-well plates and treated for 24 h with MEK162. A p-Erk in-cell Western assay was performed and maximal inhibition, relative and absolute IC50 values calculated using Excel Fit software.

Nude Mouse, HT-29 Xenograft

The effects of binimetinib on ERK phosphorylation in HT-29 human colorectal carcinoma xenograft tumours were evaluated in nude mice (Study 060304-800). Mice were implanted with tumour cells (5 x 10^6 cells, subcutaneous [SC] and the tumours were allowed to grow to 300 mm^3. Animals received a single dose of vehicle or binimetinib (3, 10 or 30 mg/kg, PO) and were sacrificed at 2, 4, 12 and 24 hours post-dose.

Target inhibition of nearly 100% was achieved at all doses of binimetinib, and 50% inhibition was maintained at 24 hours following a single dose of either 10 or 30 mg/kg binimetinib, which supports BID dosing to achieve maximum target inhibition in the mouse tumour models.

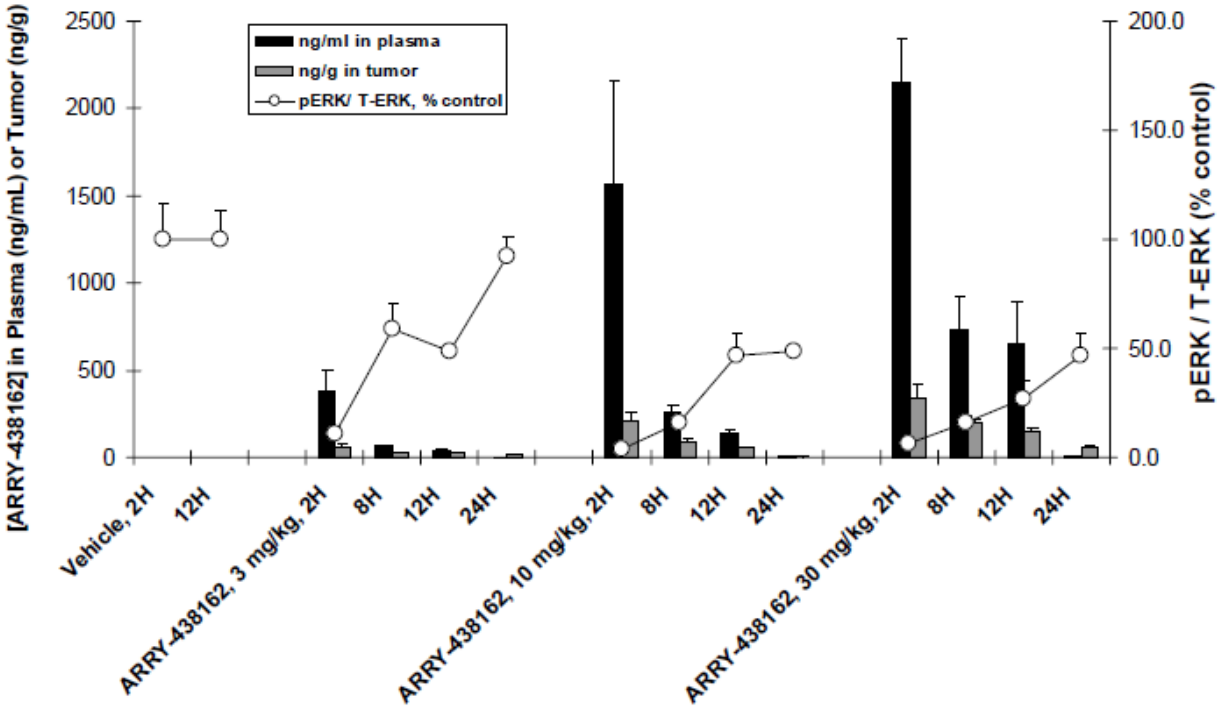


Figure 2: Effects of binimetinib on ERK Phosphorylation in HT-29 Human Colorectal Carcinoma Tumours

N = 4 mice per treatment group T-ERK = total ERK Data are mean ± SEM

Nude Mouse, A375 B-Raf-Mutant Melanoma Xenograft *(High Dose Ranging)*

The effects binimetinib on A375 human B-Raf-mutant melanoma tumour growth in nude mice were evaluated (Study RD-2010-00964). Mice were implanted with tumour fragments, and the tumours were allowed to grow to 100–150 mm^3. Animals received vehicle or binimetinib (30 or100 mg/kg, PO, BID for 14 days; or 300 mg/kg, PO BID for 3 days, weekly x 2). At the end of the treatment period, tumour growth delay for each drug treated group was assessed in comparison to the vehicle treated control group. The current summary limits itself to a description of the efficacy and tolerability after 14 days of treatment.

Oral administration of MEK162 at 30 and 100 mg/kg, BID produced tumour regression (T/C% = - 11 and -20%, respectively). In contrast, MEK162 administered at 300 mg/kg BID intermittently only caused tumour growth delay which was not statistically different from the control group (Figure 3). MEK162 treatment at all doses was well tolerated with minimal body weight loss and no treatment related deaths.

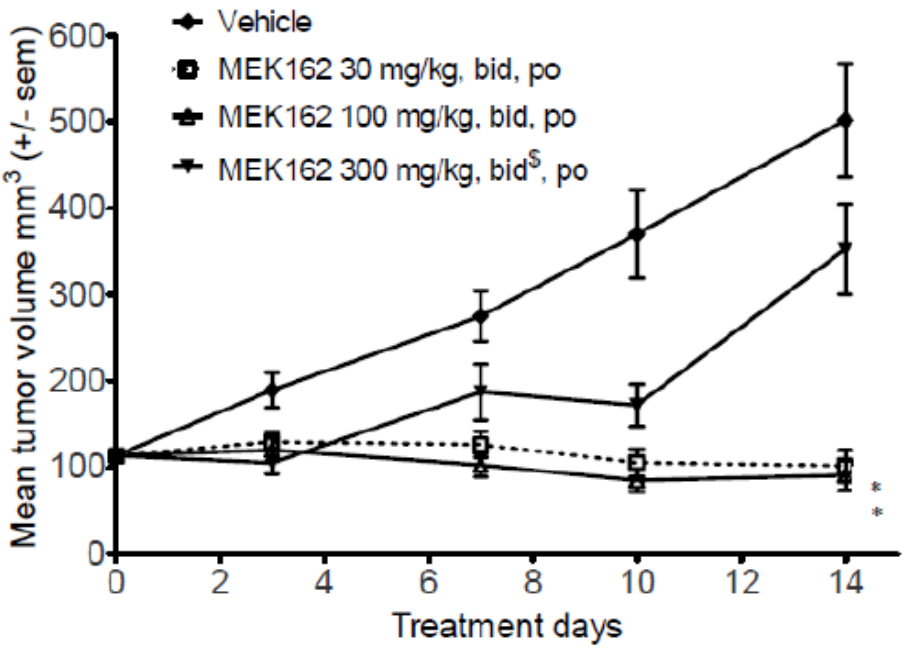


Figure 3: Effects of binimetinib on Tumour Growth in A375 Human B-Raf-Mutant Melanoma Xenografts in Nude Mice (Low Dose Ranging)

N = 12 mice per treatment group at study start
$ 300m/kg dose was administered 3 days on and 4 days off over 14 days.
**P<0.05 ANOVA Kruskal-Wallis post hoc Dunn's versus vehicle control.*

Binimetinib and Encorafenib in combination

Cell Culture

Binimetinib (ARRY-438162, MEK162) in combination with encorafenib (LGX818) with was assessed in melanoma and CRC-derived cancer cell. For each cell line, the LGX818 combination with MEK162 was compared to the combination of each agent with itself (self-crosses) as a control (Table 3).

Table 3: Summary of Synergy Evaluations for MEK162 with LGX818

Cell-line Name	Cancer Type	MEK162 IC50 (nM)	LGX818 IC50 (nM)	Syngergy Score	Best CI (at 50% inhibition)	Effect Description	BRAF	KRAS	NRAS	PIK3CA	PTEN
SW1417	CRC	24.01	15.0	2.55	1.34	Additive/Synergy	Mut	wt	wt	wt	wt
COLO 205	CRC	15.71	3.7	2.05	1.05	Additive/Synergy	Mut	wt	wt	wt	wt
LS411N	CRC	19.42	3.6	2.01	0.89	Additive/Synergy	Mut	wt	wt	wt	wt
HT-29	CRC	32.00	4.1	3.32	1.43	Additive/Synergy	Mut	wt	wt	Mut[#]	wt
RKO	CRC	>2700	560.7	1.72	0.48	Synergy	Mut	wt	wt	Mut	wt
OUMS-23	CRC	>2700	>2700	0.17	nc	Additive	Mut	wt	wt	wt	Mut[§]
HuTu 80	CRC	>2700	>2700	1.75	0.64	Additive/Synergy	wt	wt	wt	wt	wt
CW-2	CRC	>2700	>2700	0.14	nc	Additive	wt	wt	wt	wt	wt
NCI-H716	CRC	>2700	>2700	0.93	nc	Additive	wt	wt	wt	wt	wt
C2BBe1	CRC	>2700	>2700	0.50	0.63	Additive	wt	wt	wt	wt	wt
SNU-C1	CRC	10.2	>2700	0.35	2.23	Additive	wt	wt	wt	wt	wt
KM12	CRC	231.6	>2700	0.19	1.30	Additive	wt	wt	wt	wt	wt
A-375	Melanoma	20.0	5.8	1.20	0.87	Additive/Synergy	Mut	wt	wt	wt	wt
COLO 741	Melanoma	1190.4	32.6	1.45	0.27	Additive/Synergy	Mut	wt	wt	wt	wt
COLO-800	Melanoma	50.5	7.9	2.67	0.84	Additive/Synergy	Mut	wt	wt	wt	wt
IGR-1	Melanoma	893.0	167.6	3.81	0.02	Synergy	Mut	wt	wt	wt	wt
IGR-37	Melanoma	82.8	17.6	1.03	0.70	Additive/Synergy	Mut	wt	wt	wt	wt
K029AX	Melanoma	78.8	12.8	2.59	0.73	Additive/Synergy	Mut	wt	wt	wt	wt
LOX IMVI	Melanoma	>2700	>2700	5.99	0.28	Synergy	Mut	wt	wt	wt	wt
A2058	Melanoma	978.0	1486.1	2.07	0.34	Synergy	Mut	wt	wt	wt	Mut
IGR-39	Melanoma	>2700	>2700	0.70	nc	Additive	Mut	wt	wt	wt	Mut
RPMI-7951	Melanoma	>2700	>2700	1.02	nc	Additive	Mut	wt	wt	wt	Mut[§]
SK-MEL-24	Melanoma	892.2	776.0	1.87	0.66	Additive	Mut	wt	wt	wt	Mut[§]
UACC-62	Melanoma	47.0	3.7	1.26	0.93	Additive/Synergy	Mut	wt	wt	wt	Mut
COLO 792	Melanoma	182.5	>2700	0.90	1.29	Additive	wt	wt	wt	wt	wt
HMCB	Melanoma	>2700	>2700	2.86	0.04	Synergy	wt	wt	wt	wt	wt
MeWo	Melanoma	>2700	>2700	2.60	0.25	Synergy	wt	wt	wt	wt	wt
SK-MEL-31	Melanoma	>2700	1032.0	0.93	0.80	Additive	wt	wt	wt	wt	Mut

Nude Mouse, HMEX1906 (BRAFV600E) Mutant Human Melanoma Primary Xenograft

This study was designed to evaluate whether combining binimetinib and encorafenib would prevent the emergence of resistance in the HMEX1906 (BRAFV600E) PDX model. MEK162 was evaluated at two doses that approximate the clinically-relevant doses, and LGX818 was evaluated at a dose that was anticipated to result in resistance within 1 to 2 months. There were 6 treatment groups: vehicle (1% CMC/0.5 % Tween 80 in water), binimetinib (MEK162; 3 or 10 mg/kg, PO, BID), encorafenib (LGX818; 3 mg/kg, PO, BID) and 2 combination treatment groups with binimetinib (MEK162, 3 or 10 mg/kg, PO, BID) plus encorafenib (LGX818; 3 mg/kg, PO, BID).

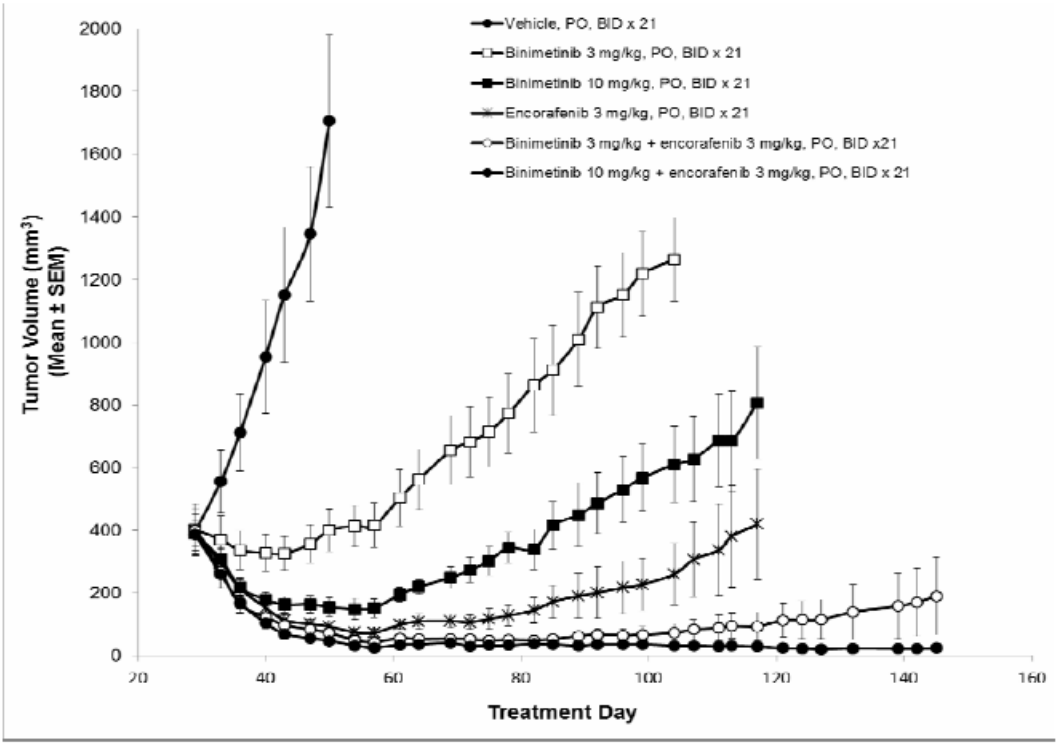


Figure 4: Efficacy of Encorafenib and Binimetinib as Single Agents and in Combination in the HMEX1906 (BRAFV600E) PDX Model

N = 8 mice per treatment group at study start

Tumour growth curves end when 2 or more mice have been removed from the study due to tumour burden.

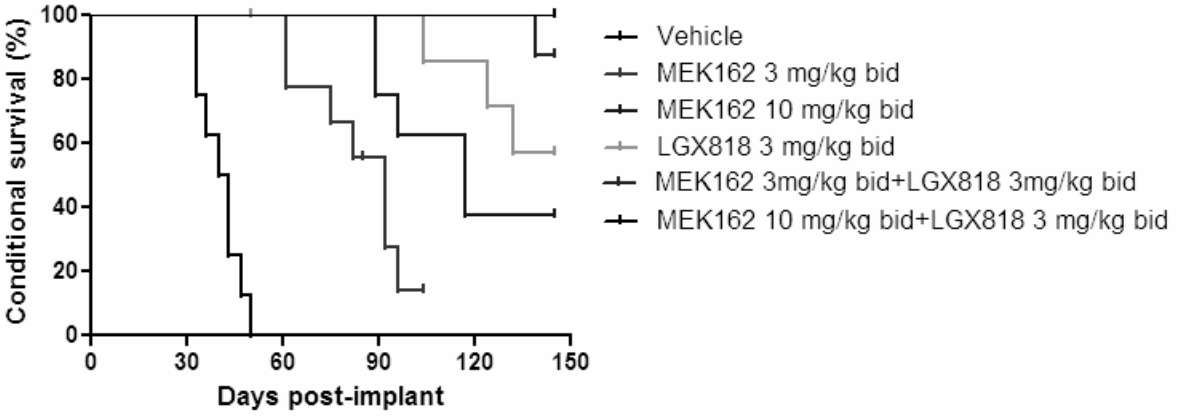


Figure 5: Survival Analysis of Binimetinib and Encorafenib as Single Agents and in Combination in the HMEX1906 (BRAFV600E) Melanoma PDX Model

Median survival for the Vehicle control, 3 mg/kg binimetinib and 10 mg/kg binimetinib groups was 42 days, 92 days and 117 days, respectively. Median survival was not reached for the 3 mg/kg encorafenib and both combination groups. There was also a significant increase in survival for the 10 mg/kg binimetinib + 3 mg/kg encorafenib combination group compared to each single agent treatment group, however there was no significant difference between the 3 mg/kg binimetinib + 3 mg/kg encorafenib and single-agent encorafenib treatment groups.

Secondary pharmacodynamic studies

Binimetinib was tested against a panel of 219 kinases. Other than MEK1, 1 µM binimetinib did not inhibit any of the other kinases by more than 30%. With 10 µM binimetinib, only calcium/calmodulin kinase IV (31%), Fer (fps/fes related) tyrosine kinase (phosphoprotein NCP94) (38%) and MEK1 (92%) were inhibited by more than 30%.

Table 4: Kinase Activity and Receptor Screening Assay and Off-target activity

Species/ Strain	Method of Admin.	Organ Systems Evaluated	Doses and Duration	Gender and No. per Group	Noteworthy Findings
Selectivity Enzymatic activity	In vitro	219 kinases Selectivity	1 or 10 µM	NA	*1 µM binimetinib did not inhibit any of the other 219 kinases by more than 30%. *Binimetinib is selective
Off target activity	In vitro	Enzymes, receptors, transporters, channels	Range of 12 concentrations	NA	Binimetinib did not show an activity of greater than 50% inhibition or activation at 10 µM in any of the targets tested. The only activity found was in the bile salt export pump (BSEP) vesicular uptake assay (IC_{50} = 87 µM). Even though the IC_{50} for BSEP is quite high, this could still become relevant in a therapeutic situation if the local free concentration of the compound in the liver is high. None of the suicidality targets were hit.

Safety pharmacology programme

Safety pharmacology studies performed with binimetinib as a single agent are shown in Table 5.

Table 5: Overview of the safety pharmacology studies

Organ Systems Study Number	Species /Strain	Method of Administration	Doses a (mg/kg)b	Number of Animals per Group (M/F)	Noteworthy Findings
Neurobehavioral Function ***1140-012***	Rat, Sprague-Dawley	PO	0, 10, 30 or 100	15/15	• No significant effect up to 100 mg/kg • NOEL > 100 mg/kg
hERG Channel ***050726.BCP***	HEK293 cells	In vitro	Up to 30 µM	NA	hERG channel inhibition was 30% at 30µM
hERG Channel ***pcs-1414541***	HEK293 cells	In vitro	Up to 100 µM, AR00426032 (active metabolite)	NA	hERG channel inhibition was 11% at 100µM for AR00426032
Cardiovascular Function ***JAY00033***	Monkey, Cynomolgus	PO	0, 1, 3 or 10	6/0	No significant effects noted in MABP, HR or ECG waveform QT or QTc data • NOEL = 10 mg/kg

Respiratory Function ***1140-011***	Rat, Sprague-Dawley	PO	0, 10, 30 or 100	12/0	• No significant effect up to 100 mg/kg • NOEL =100 mg/kg
Gastric Secretion ***AA30228***	Rat, Sprague-Dawley	PO	0, 10, 30 or 100	10/0	Slight, dose-related decreases in gastric acid secretion and gastric volume at 10 and 30 mg/kg • No significant effects at 100 mg/kg • NOEL = 100 mg/kg
Gastric Motility ***1140-013***	Rat, Sprague-Dawley	PO	0, 10, 30 or 100	10/10	No significant effect up to 100 mg/kg • NOEL = 100 mg/kg
Renal Function ***1140-010***	Rat, Sprague-Dawley	PO	0, 10, 30 or 100	0/10	• No significant effect up to 100 mg/kg • NOEL = 100 mg/kg
Immune Modulation ***PT#1105452***	Mouse/CD-1; Mouse/ C57/Bl6 (LPS challenge only)	PO	LPS Challenge: 0, 3, 10 or 30 (QD for 3 days) • *S. aureus* or *C. albicans* Challenge: 0, 10 , 30 or 100 (QD for 7 days)	8/0	• LPS Challenge: Non-significant protective effect on survival at 10 and 30 mg/kg • *S. aureus* or *C. albicans* Challenge: Significant protective effect on survival at 10 and 30 mg/kg in the *S.aureus* study and at 30 mg/kg in the *C. albicans* study
Wound Healing ***PT#1077057***	Mouse/CD-1	PO	0, 3, 10 or 30 (BID for 10 days)	12/0	No effects on wound healing

a Single dose unless specified otherwise
b All studies were conducted using ARRY-438162 and all dose levels refer to active compound. All doses are in units of mg/kg unless otherwise specified.
NA = Not Applicable

Pharmacodynamic drug interactions

Pharmacodynamic drug interactions were not submitted (see non-clinical discussion).

2.3.3. Pharmacokinetics

Absorption

The table below shows a summary of the PK data in various animal models.

Table 6: PK data in mice, rats and monkeys following oral of IV administration of binimetinib

Study ID	Type of Study	Species N/Gender	Route, Dose	Results
DM05-049	**Single dose** BV of free base	**Rats** 3M	**Oral** 10; 30; 100 mg/kg BW **IV** 1 mg/kg BW	Following a single IV dose to male rats, the mean AUC_{inf} value was 10.0 ± 0.9 µg-hr/mL. The mean plasma clearance (CL_{inf}), $t_{1/2}$ and steady-state volume of distribution values were 1.67 mL/min/kg, 2.37 hr, and 189 mL/kg, respectively. The mean AUC_{inf}, t1/2 and mean residence time (MRT) were 10.0 µg-hr/mL, 2.37 hours and 1.89 hours, respectively. Following a single PO dose the mean C_{max} values were 5.38, 11.9 and 20.2 µg/mL for doses of 10, 30, and 100 mg/kg, respectively. The mean oral bioavailability values were 76.4%, 53.1%, and 45.5%, respectively.
DM05-050	**Single and repeated dose** BV of free base	**Monkeys** 3M	**IV** 3 mg/kg BW (single) **Oral** 1; 3; 10 mg/kg BW (single or 5 Days)	Following single IV dose the mean AUC_{inf}, plasma clearance, steady-state volume of distribution (Vss), and t1/2 were 6.60 ± 1.82 µghr/ mL, 8.05 ± 2.60 mL/min/kg, 1.04 ± 0.58 L/kg, and 5.48 ± 2.11 hr, respectively. Following single po doses the mean plasma AUC_{0-t} values were 0.564 ± 0.030, 2.50 ± 0.701, and 7.87 ± 1.39 µg-hr/mL for the 1-, 3-, and 10-mg/kg doses, respectively. The mean plasma C_{max} values were 0.049 ± 0.012, 0.330 ± 0.239, and 0.898 ± 0.483 µg/mL while the mean plasma T_{max} values were 2.83, 2.33, and 2.17 hours for the 1-, 3-, and 10-mg/kg doses, respectively. The $t_{1/2}$ was 8.48 ± 0.72 hr, 7.7 ± 0.95 hr, and 7.93 ± 0.27 hr for the 1-, 3-, and 10-mg/kg doses, respectively. The oral bioavailability (F) values were 26.7 ± 1.4%, 39.4 ± 11.1% and 37.2 ± 6.6%, respectively. Following oral dosing for 5 days the plasma AUC_{0-t} values on Day-1 were 0.417, 1.28 and 4.38 µg-hr/mL. The AUC_{0-t} values on Day-5 were nearly the same at the 1 and 3 mg/kg doses, but show a slight trend for

Study ID	Type of Study	Species N/Gender	Route, Dose	Results
				decreased exposure in two monkeys at the 10-mg/kg doses (2.69 µg-hr/mL). The mean plasma C_{max} and T_{max} values were similar on D1 and D5 at all doses. The mean oral bioavailability values for each dose and on Day-1 was approximately 20% across all doses of. After 5 days dosing at 10 mg/kg there was an apparent decrease in oral bioavailability (to 12.7%) when determined with respect to the mean dose-normalized IV AUC_{0-t}.
DM09-001	**BV of oral Binimetinib Capsules or Tablets**	**Monkeys** 6 M Parallel design	**Oral** 1mg/kg BW	Capsules exhibited a mean C_{max} of 291 ± 332 ng/mL, a mean apparent T_{max} of 1.67 ± 1.21 hr and a mean AUC_{0-inf} of 1,110 ± 514 ng-hr/mL. Tablets: the resulting mean dose normalized C_{max} value was 428 ± 231 ng/mL, the mean apparent T_{max} was 1.17 ± 0.68 hr and the mean dose normalized AUC_{0-inf} was 1,710 ± 784 ng-hr/mL. In comparison to the capsule formulation, the mean dose normalized values of C_{max} and exposure (AUC_{0-inf}) are greater for the tablet formulation but the differences were not statistically significant due to intersubject variability.
DM09-043	**Single dose** PK of free base and two metabolites (N-desmethyl and amide metabolite)	**Nude Mice** 30 F	**IV** 1 mg/kg BW **Oral** 3; 10; 30 mg/kg BW Or 100 or 300	**IV**: AUC_{inf} 2,916 ng-hr/mL, CL 5.72 mL/min/kg, Vss 0.29 L/kg, $t_{1/2}$ 4.80 hr, and MRT 0.85 hr. **Oral:** The absolute oral bioavailability in athymic female nu/nu NCr mice at 3, 10, 30, 100, or 300 mg/kg was approximately 43, 47, 54, 42, and 29%, respectively. The mean C_{max} and AUC indicated that oral exposure was approximately dose proportional from 3 to 100 mg/kg. For AUC values ref. to text. Considerable concentrations of the *N*-desmethyl (AR00426032) or amide (AR00426618) metabolites were found in the plasma of each group of animals at each dose level. Plasma exposure of

Study ID	Type of Study	Species N/Gender	Route, Dose	Results
				AR00426032 (M3) increased with increasing dose and accounted for approximately 25, 21, 17, 11, and 7% of the plasma exposure of ARRY-438162. Plasma exposure of AR00426618 increased with increasing dose and accounted for approximately 52, 30, 56, 27, and 14% of the plasma exposure of ARRY-438162.
DM09-044	**Two doses** PK of free base and two metabolites (N-desmethyl and amide metabolite) After antibiotic treatment for 5 days in order to deplete gut bacteria	**Nude Mice** 3 F /group	**Oral** 30 mg/kg twice on day 6	Plasma concentrations of ARRY-438162 and AR00426032 were comparable between the animals in this study and those in study DM09-043. However, plasma concentrations of AR00426618 (amide metabolite) were significantly lower in the present study than in study DM09-043. The plasma concentrations of AR00426618, together with the decreased bacterial content in feces, indicate that the formation of AR00426618 in the nude mouse is most likely due to gut bacteria. (see section 3.4. metabolism).
Dmpk-1100228	**Single dose** PK of ^{14}C-MEK162	**Rats** 3 M	**IV** 1mg/kgBW **Oral** 4mg/kgBW	**IV:** The blood radioactivity concentrations decreased rapidly to ~19% at 1 h and <1% at 24 h, as compared to the mean total radioactivity concentrations (4550 ngEq/mL) at 5 min. The plasma and blood profiles of radioactivity were bi-phasic. Radioactivity concentrations in blood were slightly lower than that in plasma, indicating the plasma had a higher affinity for the radioactivity. This is consistent with the in vitro higher distribution to plasma in rats .The concentration of MEK162 in plasma appeared to be biphasic. The mean terminal half-life of was 6.6 hours. The mean C_{max} and AUC_{inf} were 6990 ng/mL and 5920 ng·h/mL respectively. The mean volume of distribution at steady state (Vss) was low (0.618 L/kg). The systemic plasma clearance of the compound (CL) was low with a mean value of 0.173 L/h/kg comparing to rat hepatic blood flow. **Oral:** T_{max} in plasma was 0.33 h,

Study ID	Type of Study	Species N/Gender	Route, Dose	Results
				suggesting a fast absorption. Based on the dose normalized plasma radioactivity AUC_{inf} and total radioactivity recovery in urine after i.v. and oral dose, the percentage of absorption of MEK162 was estimated to be ~50%. The bioavailability for MEK162 was calculated to be 47.1%, indicating minor first pass effect.
Dmpk-1100796	**Single dose PK of ^{14}C-MEK162**	**Monkeys** 3 M oral 2M IV.	**IV** 1 mg/kgBW **Oral** 3 mg/kgBW	**IV:** ref to study amendment 1: Radioactivity in blood: C_{max} 3510 ngEq/ml AUC_{last} (ngEq•h/mL) 4420 Radioactivity in plasma: C_{max} 6790 AUC_{last} 8170 MEK162 in plasma: C_{max} 5240 AUC_{last} 8170 **Oral:** Following a 3 mg/kg MEK162 was rapidly absorbed with a T_{max} at 0.67 h. The overall oral absorption was estimated to be 50% ~ complete, based on plasma radioactivity concentration and urine recovery after IV and oral dose, while the bioavailability was calculated to be 48%.

Distribution

Tissue distribution

Whole body autoradiography

A tissue distribution study was performed for drug-derived carbon-14 material using quantitative whole body autoradiography (DM07-001) following a single oral dose of [14C]binimetinib (30 mg/kg) to fasted male albino (Sprague-Dawley) and pigmented (Long- Evans) rats. Drug-derived radioactivity was absorbed and widely distributed to tissues of albino and pigmented rats, with maximum concentrations in most tissues observed 1 to 2 hours post-dose.

Table 7: Quantitative Tissue Distribution of Drug-Related Material Using Whole-Body Autoradiography Following A Single Oral Dose of [14C]ARRY- 438162 (30 mg/kg) to Male Long-Evans and Sprague-Dawley Rats and Human Radiation Dosimetry Prediction

Species		Albino Sprague-Dawley Rat						Pigmented Long Evans Rat			
Gender (M/F) Number of animals		M n = 6 (1/timepoint)						M n = 4 (1/timepoint)			
Feeding Condition		Fasted overnight (12 h prior to dose and 4 h post-dose administration).						Fasted overnight (12 h prior to dose and 4 h post-dose administration).			
Vehicle/Formulation		1% CMC and 0.5% Tween 80						1% CMC and 0.5% Tween 80			
Method of Administration		PO/single dose						PO/single dose			
Dose (mg/kg)		30						30			
Radionuclide		[^{14}C]ARRY-438162						[^{14}C]ARRY-438162			
Specific Activity		42.3 mCi/mmol						42.3 mCi/mmol			
Sampling time		1, 2, 4, 8, 24, 168 h						2, 8, 24, 168 h			
		Concentration (µgEq/g tissue)									
		Albino Rat						Pigmented Rat			
Tissues type	Tissue	1 h	2 h	4 h	8 h	24 h	168 h	2 h	8 h	24 h	168 h
Vascular/ Lymphatic	Blood (cardiac)	14.7	6.68	2.58	1.87	0.536	BQL	13.6	6.32	0.430	BQL
	Bone Marrow	4.54	2.08	1.58	0.926	0.480	BQL	5.08	2.49	0.569	BQL
Excretory/ Metabolic	Bile (in duct)	283	86.5	80.8	48.3	4.76	BQL	123	110	13.5	BQL
	Renal Cortex	18.4	13.5	12.8	2.54	1.26	BQL	18.7	7.83	1.24	BQL
	Renal Medulla	25.0	8.41	14.0	2.16	0.920	BQL	21.1	7.52	1.47	BQL
	Liver	11.0	7.50	6.74	3.21	1.94	BQL	13.9	9.09	3.27	0.348
	Urinary Bladder	6.88	19.5	3.32	0.718	1.16	BQL	16.3	3.77	0.975	BQL
Additional Information LLOQ = 0.00084264 µCi/g /0.002506 µCi/µg = 0.336 µg equivalent/g tissue ULOQ = 8.177 µCi/g / 0.002506 µCi/µg = 3262.969 µg equivalent/g tissue											

M: male; F: Female; IV: intravenous; PO: per os; CMC: carboxymethylcellulose; LLOQ: Lower Limit of Quantification; ULOQ : Upper Limit of Quantification; BQL: Below Limit of Quantification i.e below the LLOQ or could not be visualized on autoradioluminograph due to BQL radioactivity; Eq: equivalent; NA: not applicable

An in vitro study subsequently confirmed that MEK162 and the active N-desmethyl (M3) metabolite both have low affinity to melanin (Report DMPK R1100541). There was no evidence of CNS penetration (i.e., all measurements in this compartment were below the limits of quantification). There was no accumulation of radioactivity in various glands (testes, thyroid, pituitary gland, pancreas, harderian gland and adrenal gland). The blood-to-plasma concentration ratios ranged from 0.652 to 0.994 across species (0.718 in humans).

Protein binding and distribution in blood cells

The distribution of [14C]binimetinib was determined in blood and plasma across multiple preclinical species and humans (DMPK R1100217). The plasma protein binding of binimetinib was high (> 96%) in all species tested except in the dog where the plasma protein binding was moderate (84%).

Metabolism

In vitro metabolism

Binimetinib was shown to be both chemically and metabolically stable in the plasma from rats, monkeys and human at 37°C (DM05-027). The metabolic stability of binimetinib in hepatocytes from CD-1 mice, Sprague-Dawley rats, beagle dogs, cynomolgus monkeys and humans was characterized as low to moderate with hepatic extraction ratios (ER) < 30% predicted for all species.

The in vitro metabolism of binimetinib was studied in the presence of hepatic microsomes and hepatocytes from CD-1 mice, Sprague-Dawley rats, beagle dogs, cynomolgus monkeys, and humans (DM05-038). The most abundant metabolites produced from human hepatocyte incubations were products of direct glucuronidation of binimetinib.

In incubations of [14C]binimetinib with human hepatocytes the relative contributions of glucuronidation (M10.2 and M10.9), hydrolysis (M15.9), formation of M10.5, and the oxidative N-desmethylation (M3), to the overall metabolism of [14C]binimetinib were 45.1%, 5.1%, 5.9%, and 2.4%, respectively. The primary oxidative metabolite in human hepatocyte incubations was N-desmethyl binimetinib (M3). Finally, no metabolites were observed in incubations of [14C]binimetinib with human liver cytosol fractions, and no additional metabolites were observed in incubations with S9 fractions of human liver supplemented with NAPDH.

CYP Studies

Experiments to determine which CYP enzymes were responsible for the oxidative metabolism of [14C]binimetinib were performed using insect cell membrane preparations containing individual recombinant CYP and flavin monooxygenases (FMO) enzymes. [14C]binimetinib metabolism above control levels was detectable in incubations with CYP1A1, CYP1A2, CYP2C19 and CYP3A4. The oxidative metabolite M3, found in HLM, was found to be formed by CYP1A1, CYP1A2 and CYP2C19. A of binimetinib oxidative metabolites (P8.5, M18.2, M23.0 and M24.5) were observed in CYP3A4 incubations that were not detected following human hepatocytes or microsomal incubations.

An in vitro study using recombinant human CYP enzymes showed that the enzymes capable of metabolizing binimetinib were CYP1A1, CYP1A2, CYP2C19, and CYP3A4 (DMPK R1100166). CYP1A2 and CYP2C19 catalyzed the formation of the active metabolite, AR00426032 (M3). Further studies were conducted to determine the contribution of CYPs to the oxidative metabolism of binimetinib (DMPK R1100166). The inhibitor of CYP1A2, furafylline, decreased [14C]binimetinib oxidative metabolism in HLM (i.e., formation of M3) by ~62% with an approximate IC50 of 2.4 µM. The maximal percent inhibition observed with ticlopidine (CYP2B6/CYP2C19 inhibitor) was ~41%. In contrast, the inhibitors ketoconazole (CYP3A4), azamulin (CYP3A), quinidine (CYP2D6), montelukast (CYP2C8), and sulfaphenazole (CYP2C9) had little effect on total [14C]binimetinib metabolism; with maximal observed percent inhibitions of 0.3-9%. The percent contribution of both CYP1A2 and CYP2C19 to total hepatic oxidative microsomal metabolism of binimetinib was estimated to be equivalent (~50%).

CYP Inhibition

Binimetinib was assessed as a potential inhibitor of cytochrome P450s. Binimetinib was a weak inhibitor (IC50 ~ 50 µM) of CYP1A2 and CYP2C9 activity. Very little or no inhibition of CYP2A6, CYP2C8, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 was observed at binimetinib concentrations up to 100 µM. Binimetinib showed no apparent time dependent inhibition of CYP1A2, CYP2C9, CYP2D6 or CYP3A4/5 at binimetinib concentrations up to 50 µM. Binimetinib showed relatively potent inhibitory activity for CYP2B6 (IC50 of 6 µM and a Ki of ~1.73 µM; and was similar when adjusted for microsomal protein binding, Ki,u of 1.67 µM).

CYP Induction

Binimetinib was investigated as an in vitro inducer of cytochrome P450 enzymes in human hepatocytes in several studies. Significant induction of CYP3A4 activity was not observed in a human DDI study, where multi-day administration of binimetinib (30 mg, BID) did not significantly affect the exposure of the CYP3A4 probe midazolam.

UGT enzymes

Experiments to determine which UGT enzymes were predicted to catalyze the conjugative biotransformation of binimetinib to the direct glucuronides, M10.2 and M10.9, were performed with a panel of recombinant UGT enzymes. By this approach, UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4 and UGT2B7 were capable of generating both the binimetinib -glucuronide conjugates, M10.2 and M10.9.
UGT1A1 was shown to be the major contributor (90%) to the formation of the direct glucuronide M10.9 from binimetinib in HLMs. UGT1A3 and UGT1A9 contributed 3% and 7%, respectively, to the glucuronidation activity.

UGT Inhibition

Binimetinib was found to be a weak inhibitor of human liver microsomal UGT1A-mediated SN- 38 conjugation, with an IC50 value greater than 25 µM (DM09-035).

Table 8: Summary table of binimetinib metabolites in rat, monkey and humans

Study No	CMEK162A2102, DMPK R1100796, DMPK R1100228, DMPK R1200065											
Study System	See referenced reports											
Objective	Metabolite Identification of [14C]MEK162 Metabolism in the Plasma, Urine and Feces From Rats, Cynomolgus Monkeys and Humans											
Metabolite	Putative Structural Description	MH+ m/z	Plasma			Urine			Feces			Bile
			Rat	Monkey	Human	Rat	Monkey	Human	Rat	Monkey	Human	Rat
M8.0	Indirect glucuronide of M4	555	-	+	+		+	+	+			+
M10.2	Direct glucuronide	617	-	++	+	+	+	+	-	-	-	+
M10.5	Indirect glucuronide of M4	555	+	+	+	+	+	+	-	-	-	+
M10.9	Direct glucuronide	617	+	+	+	+	+	+	-	-	-	+
M11.0	Glucuronide of M17.0	545	-	+	-	-	+	-	-	-	-	-
M11.1	Oxidation	457	+	-	-	+	-	-	+	-	-	-
M13.2	O-glucuronide conjugate of M4	575	-	-	-	-	+	-	-	-	-	-
M14	Direct glucose conjugate	605	-	-	-	+	-	-	+	-	-	-
M14.6	Glucuronide of M3	603	-	-	+	+(BDC)	-	+	-	-	-	+
M15.1	Glucuronide of M17.0	541	-	-	+	+(BDC)	-	+	-	-	-	+
M3;AR00426032	N-desmethyl	427	+	+	+	+	+	+	+	+	+	-
M15.7	Glucuronide	617	-	-	+	+(BDC)	-	-	-	-	-	+
M15.9	Carboxylic acid	382	+	+	+	+	+	+	+	+	+	-
M16.0	Glucuronide of M3	603	-	-	+	+(BDC)		+				+
MEK162	Parent drug	441	++	++	++	+	+	+	+	+	+	+
M17.0	N-demethylation of M4	367	+	++	+	+	+	+	+	+	+	-
M18.2	Dehydrogenated M4	381	-	+	-	+	+	-	+	+	-	-
M18.9	Indirect glucuronide of M15.9	544	-	-	+	-	-	+	-	-	-	-
M4	Amide (ethane-diol cleavage product)	381	+	+	+	+	+	+	+	+	+	
M19.5	Glucuronide of M15.9	558	-	-	+	-	-	+	-	-	-	+
M24.1	Monooxygenated M3	443	-	-	+	-	-	+	-	-	+	-
M24.5	Loss of NH_3 from MEK162	428	-	-	-	-	-	-	-	+	-	-

-, indicates metabolite not detected; +, indicates metabolite detected; ++ indicates metabolite detected at >10% of radioactive dose of [14C]MEK162 as circulating in plasma (only occurred monkeys).

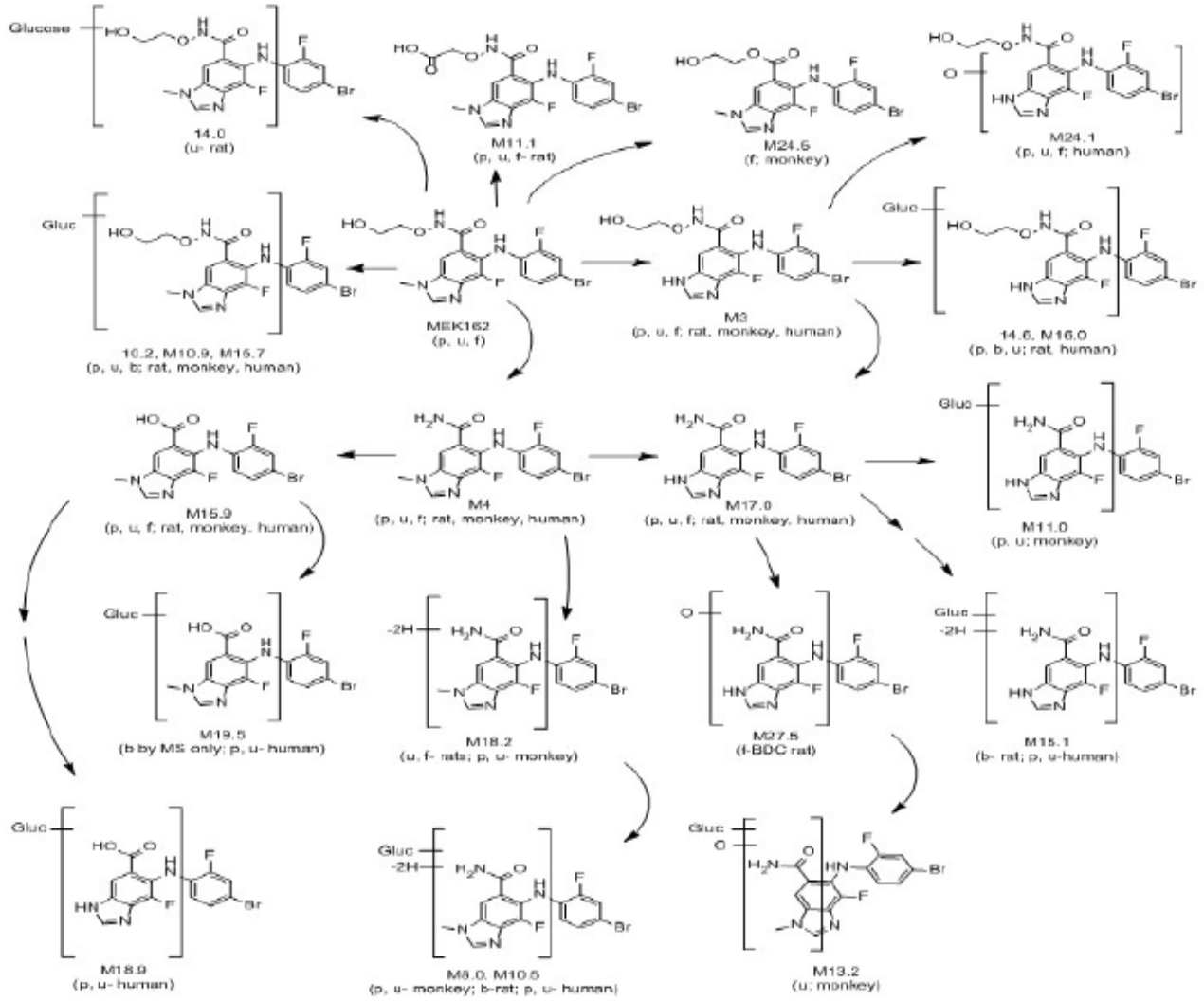


Figure 6: In vivo putative metabolic pathways of MEK162

p:plasma u:urine f:faeces/bile b:bile from BDC rats only

Excretion

Routes and extent of excretion

Following IV dosing of [14C]-binimetinib in the rat, faecal and urinary excretion accounted for 45% and 46% of total radioactivity, respectively. Approximately 15% of binimetinib was excreted unchanged in the urine and 16% in the faeces of rats. Total radioactivity in the excreta of monkey was 99% and 85% following PO and IV dosing, respectively, with an equal contribution for urinary and faecal excretory routes. The most abundant drug-related components in monkey urine included binimetinib and two direct glucuronides (M10.2 and M10.9). In monkey faeces, binimetinib and the amide metabolite (M4; ethane-diol hydrolysis product) were the most abundant entities.

Biliary excretion of binimetinib and its metabolites was investigated in bile-duct cannulated rats (n=3) (DMPK R1400168). Following either intravenous (1mg/kg) or oral dosing (4mg/kg) of [14C]binimetinib, 50% and 39.5% of the administered radioactivity was recovered in the bile, respectively. Biliary levels of M10.9 accounted for up to 90% of the radioactivity recovered in bile.

Unchanged levels of binimetinib in bile were less than 2% of the [14C]binimetinib dose administered by oral or IV routes.

2.3.4. Toxicology

Single dose toxicity

Table 9: Tabular summary of single dose toxicity

Species/Strain	Method of Administration (Vehicle / Formulation)	Doses (mg/kg)	Gender and No. per Group	Observed Maximum Nonlethal Dose (mg/kg)	Approximate Lethal Dose (mg/kg)	Noteworthy Findings
Rat, Sprague-Dawley	Gavage (1.0% CMC and 0.5% Tween80 in water/ suspension)	0, 30, 100, 300	10M/10F per toxicology group; 6M/6F per toxicokinetic group (64M/64F total)	300	>300	30 mg/kg: o M: None o F: mineralization of ovaries 100 mg/kg: o M : slight decreases in bw; significant decreases in food consumption; mild, but reversible increases in neutrophils (~2 fold) o M+F: Mineralization of glandular stomach o F: mineralization of ovaries 300 mg/kg: o M : slight decreases in bw; significant decreases in food consumption; o M+F: Mineralization of glandular stomach, mild, but reversible increases in neutrophils (2-3 fold) o F: Sparse hair on abdomen not dose-related, mineralization of ovaries • NOAEL in M: 30 mg/kg. • NOAEL in F: not determined. • Higher exposure in F (C_{max} = 13.8, 26.6, and 35.5 µg/mL versus dose) than in M (C_{max} = 10.0, 12.7, and 24.2 µg/mL). • Mean AUC_{inf} value for F was 2.2-fold higher than for M. Mean Tmax increased from 1.5 to 4.0 hours with increasing dose; no sex-related differences in Tmax.

Repeat dose toxicity

A 28-day and a 6-month repeat-dose toxicity study (including a 13 weeks subset analysis) were performed in rats. In both studies different serum and haematology parameters were evaluated including toxicokinetics in satellite animals. A recovery phase was also implemented.

Table 10 shows the design and the major findings of the 28-day toxicity study. Most of the findings were reversible after 4 weeks of recovery; irreversible findings (irrev.) are marked accordingly.

Table 10: 28-day oral gavage repeat-dose toxicity and toxicokinetic study with binimetinib in rats

Study Type	Species;	Dose	Major findings

(Study ID) GLP	Number/Dose Group	(mg/kg/day) p.o.	
28 day repeat dose toxicity + 4 week recovery (1140-007) GLP + toxicokinetics	SD rat; 10/sex/dose recovery: +5/sex/dose toxicokinetics: +6/sex/dose (treated animals only)	0 (vehicle) 30*/10 100*/30 300*/100 *protocol error: for first 3 days dosed with higher dose	**mortality:** 1♀control, 1♂MD, 1♂1♀HD hair loss (♀MD,HD) ↑neutrophils, ↑monocytes (♂HD ♀MD,HD) ↓lymphocytes (♂MD,HD ♀LD-HD) ↓eosinophils (♂LD-HD) ↓reticulocytes (♂♀HD) irrev. ↑prothrombin time (♂HD) irrev. ↑↓prothrombin time (♀LD-HD) ↓Ca (♂HD ♀MD,HD) ↑PO_4 (♂MD,HD ♀LD-HD) ↑AST (♂♀LD-HD) ↑ALT (♂MD,HD ♀LD-HD) ↑BUN (♂LD-HD ♀MD-HD) ↓albumin (♂♀MD-HD) ↑globulin (♀LD-HD) ↓albumin/globulin (♂MD,HD ♀LD-HD) ↓glucose (♀MD-HD) **skin:** scab formation, abrasion alopecia (♂HD♀MD,HD) erosion, ulcer, hemorrhage (♂HD ♀LD-HD) **femur:** ↑thickness of growth plate, osteopenia, fibro-osseous proliferation (♂HD) **femoral bone marrow:** focal necrosis (♂♀HD) **organ weights:** ↓abs. + rel. heart (♂MD,HD♀HD) ↑abs. + rel. adrenal (♂HD♀MD,HD) ↓abs. + rel. pituitary gland (♂♀HD♀MD) ↑rel. lung (♂HD) ↑rel. kidney (♀HD) ↓abs. + rel. spleen (♀MD,HD) ↓abs. liver (♂HD) ↓abs. + rel. thymus (♀HD) **irrev. (tissue and/or vascular) mineralisation of** glandular stomach (♂♀LD-HD), tongue (♂LD-HD ♀MD,HD), pituitary gland (♂♀MD,HD), ovaries (♀LD-HD), aorta (♀HD), kidney (♀LD-HD), heart (♂♀HD) **rev. (tissue and/or vascular) mineralisation of:** duodenum (♂♀HD), colon (♂ HD), kidney (♂MD,HD), lung (♂HD), pancreas (♂♀HD), Harderian glands (♂MD,HD), brain (♀HD), mandibular salivary gland (♂♀ HD), prostate gland (♂MD)
NOAEL = Ø			

abs.: absolute, ALT: alanine amino transferase, AST: aspartate amino transferase, BUN: blood urea nitrogen, HD: high dose, irrev: irreversible, MD: mid dose, LD: low dose, rel.: relative, vehicle: 1% CMC/0.5 % Tween®80 in sterile water

A 6-month repeated-dose toxicity study was subsequently performed. Table 11 shows the study design and the major findings.

Table 11: 6-month oral gavage repeat-dose toxicity and toxicokinetic study with binimetinib in rats

Study Type (Study ID) GLP	Species; Number/Dose Group	Dose (mg/kg/day) p.o.	Major findings
6 month repeat-dose toxicity study + 4 week recovery (= week 31) 13 week interim analysis + 4 week recovery (= week 18) (1140-029) GLP + toxicokinetic	SD rats 10/sex/dose for 6 month and interim analysis, each recovery: 5/sex/dose for 6 month and interim analysis, each toxicokinetics 3/sex/dose	0 (vehicle) 1 3 10	**mortality:** 2♀control, 1♀HD interim, 1♂HD terminal, 1♂HD toxicokinetic **skin:** scabbing (♂HD, ♀MD, irrev. ♀HD) ↓erythrocytes (♂HD) ↓hemoglobin, ↓platelets, ↓eosinophils, ↓large stained cells, ↓APTT (♂HD) ↑leukocytes, ↑platelets, ↑monocytes (♀HD) ↑neutrophils (♀MD,HD) ↓Na^+ (♂HD), ↑PO_4^- (♂♀HD) ↓ total protein, albumin, cholesterol (♂HD), ↑BUN (♂♀HD) ↑AP, ↑AST (♀HD) ↑albumin, ↑globulin, ↓albumin/globulin (♀HD) parathyroid hormone: ↓week 27 and week 31 (♂♀ MD,HD) vitamin D: ↓week 31 (♂MD,HD); =/↑week 27 (♂ MD,HD), ↑/=week 31 (♀MD,HD), ↓week 27 (♀ MD,HD) **organ weights:** interim: ↓abs. + rel. spleen (♂MD,HD) terminal: ↑bw (♂HD): ↓relative organ weights of brain, epididymis, heart, liver, pituitary gland, salivary gland, spleen **microscopic findings at interim:** ↑adipocytes in bone marrow of femur (irrev. ♂ MD,HD) and sternum (♂MD,HD) ↑adipocytes in bone marrow of femur (♀ LD-HD) glandular stomach: mineralisation (irrev. ♂HD) kidneys: tubular mineralisation (♀LD-HD) dilatation of uterus (♀LD-HD) skin: alopecia, erosion/ulcer,epidermal hyperplasia, inflammation (♂LD-HD, ♀HD; partial recovery of findings) **microscopic findings at terminal:** ↑adipocytes in bone marrow of femur (♂♀LD-HD) kidney: tubular mineralisation (♂LD-HD, ♀MD-HD) lung: alveolar histiocytosis (♀LD-HD) skin: alopecia, bacterial colonies, erosion/ulcer, exudate on epidermal surface , inflammation (♂ LD, ♀MD,HD recovery, but 1 ♀HD)
NOAEL ♂rats= 3 mg/kg/day (Cmax= 2.93 µg/mL, AUC_{0-24hr}= 15.2 µg.hr/mL); NOAEL ♀rats= 1 mg/kg/day (Cmax= 2.0 µg/mL, AUC_{0-24hr}= 11.0 µg.hr/mL)			

abs.: absolute, ALP: alkaline phosphatase, APPT: activated partial thromboplastin time, AST: aspartate amino transferase, BUN: blood urea nitrogen, HD: high dose, irrev: irreversible, MD: mid dose, LD: low dose, rel.: relative, vehicle: 1% CMC/0.5 % Tween®80 in sterile water

A 6-month repeated-dose toxicity study was subsequently performed. Table 12 shows the study design and the major findings.

Table 12: 6-month oral gavage repeat-dose toxicity and toxicokinetic study with binimetinib in rats

Study Type (Study ID) GLP	Species; Number/Dose Group	Dose (mg/kg/day) p.o.	Major findings
6 month repeat-dose toxicity study + 4 week recovery (= week 31) 13 week interim analysis + 4 week recovery (= week 18) (1140-029) GLP + toxicokinetic	SD rats 10/sex/dose for 6 month and interim analysis, each recovery: 5/sex/dose for 6 month and interim analysis, each toxicokinetics 3/sex/dose	0 (vehicle) 1 3 10	**mortality:** 2♀control, 1♀HD interim, 1♂HD terminal, 1♂HD toxicokinetic **skin:** scabbing (♂HD, ♀MD, irrev. ♀HD) ↓erythrocytes (♂HD) ↓hemoglobin, ↓platelets, ↓eosinophils, ↓large stained cells, ↓APTT (♂HD) ↑leukocytes, ↑platelets, ↑monocytes (♀HD) ↑neutrophils (♀MD,HD) ↓Na^+ (♂HD), ↑PO_4^- (♂♀HD) ↓ total protein, albumin, cholesterol (♂HD), ↑BUN (♂♀HD) ↑AP, ↑AST (♀HD) ↑albumin, ↑globulin, ↓albumin/globulin (♀HD) parathyroid hormone: ↓week 27 and week 31 (♂♀ MD,HD) vitamin D: ↓week 31 (♂MD,HD); =/↑week 27 (♂ MD,HD), ↑/=week 31 (♀MD,HD), ↓week 27 (♀ MD,HD) **organ weights:** interim: ↓abs. + rel. spleen (♂MD,HD) terminal: ↑bw (♂HD): ↓relative organ weights of brain, epididymis, heart, liver, pituitary gland, salivary gland, spleen **microscopic findings at interim:** ↑adipocytes in <u>bone marrow</u> of femur (irrev. ♂ MD,HD) and sternum (♂MD,HD) ↑adipocytes in <u>bone marrow</u> of femur (♀ LD-HD) <u>glandular stomach:</u> mineralisation (irrev. ♂HD) <u>kidneys:</u> tubular mineralisation (♀LD-HD) dilatation of uterus (♀LD-HD) <u>skin:</u> alopecia, erosion/ulcer,epidermal hyperplasia, inflammation (♂LD-HD, ♀HD; partial recovery of findings) **microscopic findings at terminal:** ↑adipocytes in <u>bone marrow</u> of femur (♂♀LD-HD) <u>kidney:</u> tubular mineralisation (♂LD-HD, ♀MD-HD) <u>lung:</u> alveolar histiocytosis (♀LD-HD) <u>skin:</u> alopecia, bacterial colonies, erosion/ulcer,

			exudate on epidermal surface , inflammation (♂ LD, ♀MD,HD recovery, but 1 ♀HD)
NOAEL ♂rats= 3 mg/kg/day (Cmax= 2.93 µg/mL, AUC_{0-24hr}= 15.2 µg.hr/mL); NOAEL ♀rats= 1 mg/kg/day (Cmax= 2.0 µg/mL, AUC_{0-24hr}= 11.0 µg.hr/mL)			

abs.: absolute, ALP: alkaline phosphatase, APPT: activated partial thromboplastin time, AST: aspartate amino transferase, BUN: blood urea nitrogen, HD: high dose, irrev: irreversible, MD: mid dose, LD: low dose, rel.: relative, vehicle: 1% CMC/0.5 % Tween80 in sterile water

A 28-day and a 9-month repeat-dose toxicity study were performed in Cynomolgous monkeys with nasogastric intubation of binimetinib. A recovery group and toxicokinetic measurements were implemented in each study. Table 13 and Table 14 show the study design applied and major findings noticed during these studies.

Table 13: 28-day repeated-dose toxicity and toxicokinetic study in Cynomolgous monkeys with nasogastric administration of binimetinib

Study Type (Study ID) GLP	**Species; Number/Dose Group**	**Dose (mg/kg/day) p.o.**	**Major findings**
28-day repeat-dose toxicity study +4-week recovery (JAY00028) GLP + toxicokinetic and PBMC analysis	Cynomolgous monkeys 3/sex/dose recovery: 2/sex/dose	0 (vehicle) 1 3 10	**mortality:** 1♀HD sacrificed on Day 14, 1♂HD sacrificed on Day 28 (lethargy, hypothermia, severe diarrhea, dehydration, positive hemocult, intestinal inflammation, bone marrow hypercellularity) **clinical signs:** watery stool, lethargy, hunched posture (♂♀HD) **haematology:** ↓RBC, ↓hemoglobin, ↓haematocrit, ↑reticulocytes, ↑neutrophils, ↑platelets, ↑WBC (♂♀HD) ↓MCHC (♂♀MD) **serum chemistry:** ↓albumin, ↑AST (♂♀HD) ↑globulin, ↓albumin/globin, ↑ALT, ↑BUN (♂♀MD,HD) **organ weights:** ↓rel. heart weight (♂♀HD) **macroscopic findings:** abnormal intestinal content/gas distention of colon and cecum (♂♀HD) **microscopic findings:** degeneration of absorptive mucosal epithelium, mucosal mixed cell inflammation in the cecum, colon and/or rectum (♂♀HD), erythroid hypercellularity of bone marrow (♂♀HD) (for statistical analysis data from males and females were pooled)
NOAEL for ♂ and ♀ =3 mg/kg/day (Cmax= 0.29 µg/mL, AUC_{0-12hr}= 1.48 µg.hr/mL)* *mean values			

BUN: blood urea nitrogen, bw: body weight, HD: high dose, LD: low dose, MCHC: mean corpuscular hemoglobin concentration, MD: mid dose, RBC: red blood cell count, WBC: white blood cell count, vehicle: 1% CMC/0.5 % Tween®80 in sterile water

Table 14: 9-month repeat-dose toxicity and toxicokinetic study in Cynomolgous monkeys with nasogastric administration of binimetinib

Study Type (Study ID) GLP	Species; Number/Dose Group	Dose (mg/kg/day) p.o.	Major findings
9-month repeat-dose toxicity study + 3-month recovery + Day 92 and Day 120 interim sacrifice (JAY00117) GLP + toxicokinetics and PBMC analysis	Cynomolgous monkeys 3/sex/dose for Day 92 interim and terminal 2/sex/dose for Day120 interim and recovery	0 (vehicle) 0.2 2 (only terminal and recovery) 5	**mortality:** 1♂ control found dead on Day 12, 1♀HD sacrificed on Day 155 (hunched appearance, decreased activity, dehydration, inflammation and epithelial degeneration in the large intestine) **clinical signs:** abnormal, watery feces (♂♀HD), periorbital swelling (♂LD,HD), skin alterations (♂HD,♀MD.HD) **haematology:** ↓RBC (♂HD), ↓hemoglobin (♂♀HD), ↓haematocrit (♂HD), ↓MCHC (♂HD), ↑reticulocytes (♂HD), ↑neutrophils (♂HD♀MD), ↑platelets (♀HD), ↓prothrombin time (♀HD), ↑fibrinogen (♂♀HD) **serum chemistry:** ↓albumin (♂♀HD), ↑globulin (♂MD,HD), ↓albumin/globulin (♂MD,♂♀HD), ↑triglycerides (♀HD), ↑AST (♂MD,♂♀HD), ↑ALT (♀HD), ↓ALP (♂HD), ↑creatinine (♂LD-HD♀LD,HD), ↑PO_4^- (♂♀HD), ↓calcium (♀LD,HD), ↑Na (♀LD,MD) **organ weights:** ↓rel. spleen (♂HD), ↑rel. liver (♂HD), ↓abs. + rel. thymus (♂HD), ↓rel. heart (♂MD,HD) **microscopic findings:** large intestine: degeneration of luminal epithelium, increased mononuclear or mixed cell infiltrates, mucosal hyperplasia in the cecum, colon, and/or rectum (♂♀MD,HD), liver: mixed cell infiltrates (♂♀LD,HD), bone marrow : erythroid hypercellularity (♂♀LD,HD only at Day 92 interim)
NOAEL for ♂ and ♀: 2 mg/kg/day (Cmax= 0.2 µg/mL, AUC_{0-24hr}= 1.6 µg.hr/mL)* *mean values			

Genotoxicity

Binimetinib was tested in a standard battery of in vitro and in vivo assays for genotoxicity. Tests performed are summarized in Table 15. All tests were negative.

Table 15: Overview of genotoxicity studies with binimetinib

Type of test / study ID / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results Positive / negative / equivocal
Gene mutations in bacteria / AB14DW.503.BTL / GLP	Salmonella strains TA98, 100, 1535, 1537, E. coli WP2 uvrA	+/- S9 first study: 0.015 – 5000 µg/plate second study: 15 – 5000 µg/plate	precipitation at ≥ 1500 µg/plate no relevant increase in revertant colonies
Gene mutations in mammalian cells / AB14DW.704.BTL / GLP	L5178Y TK+/- mouse lymphoma cells	4 h exposure: +/- S9 75 – 300 µg/ml 24 h exposure: +/- S9 75 – 250 µg/ml	precipitation ≥ 250 µg/ml, cytotoxicity around 50% at highest dose no relevant increase in mutant colonies or mutant frequency
chromosomal aberrations in vivo / AB14DW.123M.BTL / GLP	ICR mouse, micronuclei in bone marrow	0, 500, 1000, 2000 mg/kg, single dose, oral gavage	no relevant increase in micronuclei in PCEs no measurement of exposure, piloerection observed in high dose male animals

Carcinogenicity

The applicant did not submit carcinogenicity studies (see non-clinical discussion).

Reproduction Toxicity

Reproductive toxicity testing was limited to embryofetal development studies in pregnant rats and rabbits, respectively. All pivotal studies were performed in accordance with GLP regulations and comply with *ICH S9 Nonclinical evaluation for anticancer pharmaceuticals.*

Table 16: Overview on the study design of and the main findings in the reproductive toxicity studies in rats and rabbits

Study type / Study ID / Species / Number Female / group	Route / dose (mg/kg/d) / vehicle / dosing period / caesarean section	Major findings	NOAEL AUC Safety margin
Embryofetal development #1140-026 Rats Crl:CD(SD) 25	oral / gavage 0 – 10 – 30 – 100 1% carboxy methylcellulose + 0.5% Tween 80 in ultrapure water gd 6 - 17 gd 20	F_0: **mortality**: 1 MD due to gavage error **bw**: ↓↓ in HD **bw change**: ↓↓ in all treated groups, but in LD only during gd 6 – 9 **fc**: ↓↓ in all treated groups **necropsy**: no findings **uterine parameters**: no effects F_1: **uterine parameters**: no effects **mean fetal bw**: ↓↓ in MD + HD **total no. of foetuses with malformation(s) / no. of litters with malformed fetuses:** **0 / 0** – **3 / 2** (1 with fused cervical vertebrae neural arches + absent ribs and 1 with fused exoccipital bone, misshapen humerus, fused cervical neural arches, absent thoracal vertebrae neural arches, absent ribs, bent scapula + spine of scapula and 1 with absent thyroid) – **2 / 2** (1	F_0: < 10 mg/kg/d F_1: 10 mg/kg/d 10 mg/kg/d → AUC_{0-24}: 57 µg*h/ml → **safety margin 13.6** (based on human AUC_{0-12} of 2.1

		with retroesophageal + right sided aortic arch; 1 with misshapen kidney) – **0 / 0**	µg*h/ml)
Embryofetal development Dose range finding (DRF) # 1140-022 Rabbits Hra:(NZW)SPF Main study: 5 TK: 4	oral / gavage 0 – 3 – 10 – 30 – 100 1% carboxy methylcellulose + 0.5% Tween 80 in ultrapure water gd 6 – 18 gd 29	F_0: **mortality**: main study: 100 mg/kg/d → all does 30 mg/kg/d: 2/5 does TK component: 100 mg/kg/d → 3/4 does **clinical signs:** 100 mg/kg/d → activity ↓, thin, soft/few/absent faeces; 30, 10 + 3 mg/kg/d → soft/few/absent faeces **bw**: 100 mg/kg/d → ↓↓ 30 mg/kg/d → ↓↓ gd 16 – 21 10 mg/kg/d → ↑↑ gd 0 – 6; gd 25 - 29 **fc**: 30 + 10 mg/kg/d → ↓↓, except gd 0 – 6 for 10 mg/kg/d group, when fc was ↑↑ **necropsy**: no findings **abortions**: 30 mg/kg/d → 2 does; 10 mg/kg/d → 1 doe F_1: **postimplantation loss (%)**: 100% at 30 mg/kg/d, no data for 100 mg/kg/d **external malformation:** 1 fetus at 10 mg/kg/d with rachischisis, encephalocele, malrotated hind limb, cleft palate	F_0: 3 mg/kg/d F_1: 3 mg/kg/d 3 mg/kg/d → AUC_{0-12}: 5.9 µg*h/ml → **safety margin 2.8** (based on human AUC_{0-12} of 2.1 µg*h/ml)
Embryofetal development # 1140-023 Rabbits Hra:(NZW)SPF 23	oral / gavage 0 – 2 – 10 – 20 1% carboxy methylcellulose + 0.5% Tween 80 in ultrapure water gd 6 – 18 gd 29	F_0: **mortality**: HD: 2/23 found dead (gd 16 + 18); 4/21 euthanized in extremis (gd 20 – 22) MD: 3/23 found dead (gd 11, 13 , 15) gavage error suspected, proven for 2 rabbits with perforation pf oesophagus **clinical signs:** HD + MD: activity ↓, thin, soft/few/absent faeces (soft/few/absent faeces: 4 Co – 11 LD – 22 MD – 23 HD); red material in bedding → some related to abortions, thin (4 HD + 3 MD) **bw**: HD + MD: ↓↓ **fc**: HD + MD ↓↓; LD ↓↓ on 3 occasions, not considered to be treatment related as body weights were not affected **necropsy**: no findings **abortions**: 1 HD + 1 MD **early delivery**: 1 HD **no. of does pregnant at C-section**: 23/23 – 23/23 – 19/23 – 14/23 F_1: **postimplantation loss**: HD + MD ↑↑ **mean no. of live fetuses / doe**: HD + MD ↓↓ **mean fetal bw**: HD + MD ↓↓ **external malformation** (no. of fetuses affected / total no. of fetuses)**:** **0 – 0 – 1 / 150** with ectrodactyly, rachischisis, abnormal flexure of entire forelimb, acephaly, omphalocele – **1 / 91** with syndactyly **visceral malformation** (no. of fetuses affected / no. of litters with affected fetuses / total no. of fetuses)**:** Control: **2 / 2 / 217** (1/1 with absent thyroid + 1/1 with dilated aortic arch, microphthalmia, absent	F_0: 2 mg/kg/d F_1: 2 mg/kg/d no TK values for 2 mg/kg/d available → TK from DRF study → 3 mg/kg/d → AUC_{0-12}: 5.90 µg*h/ml → **safety margin: ≤ 2.8** (based on human AUC_{0-12} of 2.1 µg*h/ml)

		gallbladder, discontinuous interventricular septum) LD: **1/1/199** (malpositioned + malrotated kidney) MD: **4/4/150** (1 with malpositioned , malrotated kidney; 1 with dilated aortic arch, discontinuous interventricular septum; 1 with dilated aortic arch, constricted ductus arteriosus; 1 with absent common carotid artery, malpositioned heart, transposition of great vessels, small pulmonary trunk, absent pulmonary valve, absent thyroid) HD: **13/8/91** (3/1 with dilated aortic arch, constricted ductus arteriosus, discontinuous interventricular septum, small pulmonary trunk; 2/1 with dilated aortic arch, constricted ductus arteriosus, discontinuous interventricular septum; 1/1 discontinuous interventricular septum ; 2/1 with dilated aortic arch, distended ureter; 1/1 with dilated aortic arch, constricted ductus arteriosus, discontinuous interventricular septum, small pulmonary trunk; 1/1 malpositioned adrenal; 2/1 absent kidney + ureter; 1/1 with discontinuous interventricular septum) **skeletal malformations** (no. of fetuses affected / no. of litters with affected fetuses / total no. of fetuses): Control: **5/5/217** (1/1 with fused sternum + jugal bone and misshapen maxilla + premaxilla; 1/1 with fused cervical neural arches; 1/1 with branched ribs; 1/1 with fused jugal bones; 1/1 with fused jugal bones; 1/1 with extra + misshapen thoracic arches) LD: **3/3/199** (2/2 with fused sternebrae; 1/1 with fused jugal bones) MD: **5/3/150** (1/1 with fused sternebrae; 3/1 with fused jugal bones; 1/1 with bent clavicle, misshapen exoccipital bone, absent metacarpals + phalanges) HD: **6/6/91** (1/1 with fused sternebrae; 1/1 with accessory nose bone; 1/1 with discontinuous ribs; 2/2 with fused jugal bones; 1/1 with fused costal cartilage)	

gd = gestation day; Co = control; LD = low dose group; MD = mid dose group; HD = high dose group; m = male; f = female; bw = body weight(s); fc = food consumption; ↓↓ = significant decrease(d); ↑↑ = significant increase(d)

Toxicokinetic data

For the 28-day toxicity study in the rat, no NOAEL could be identified. Exposure multiples at the LOAEL were about 8 to 14. The exposure multiple for the 6-month repeat-dose toxicity study in the rat is approximately 3 for males and females. Similar exposure multiples but different NOAELs for males and females are due to the generally higher exposure of female rats compared to males.

Table 17: Animal to human exposure multiples at the NOAEL, respectively LOAEL of the different pivotal toxicity studies performed for binimetinib in rats, monkeys and rabbits

Study	NOAEL or LOAEL (mg/kg/day	Animal to Human Exposure Multiples
Single dose toxicity rat (1140-006)	NOAEL ♂= 30	**7.1**
	LOAEL ♀= 30	**41.9**
28-day repeat-dose toxicity rat (1140-007)	LOAEL ♂= 10	**7.6**
	LOAEL ♀= 10	**13.6**
6-month repeat-dose toxicity rat (1140-029)	NOAEL ♂= 3	**3.6**
	NOAEL ♀= 1	**2.6**
28-day repeat-dose toxicity monkey (JAY00028)	NOAEL ♂= 3	**0.5**
	NOAEL ♀= 3	**0.9**
9-month repeat-dose monkey (JAY00117)	NOAEL ♂= 2	**0.4**
	NOAEL ♀= 2	
Embryo-fetal development rat (1140-026)	NOAEL ♀= 10	**13.6**
Embryo-fetal development rabbit (1140-22)	NOAEL ♀= 2	**2.8**

***$AUC_{0\text{-}12hr}$, **mean from ♂♀**

Phase I animals were treated from postnatal day (PND) 10 to PND 16, while Phase II animals received binimetinib orally from PND 10 to PND 40. The following table provides an overview on the study design and the main findings of the juvenile toxicity study.

Table 18: Main findings of the juvenile toxicity study in rats

Study type/ Study ID / Species / Number rats/sex/ group	Route / dose (mg/kg/d) / vehicle / dosing period	Major findings
Juvenile toxicity study #9000303 Rats Crl:CD(SD) **Phase I:** main study:6 TK (PND 10 + 16): 2f+2f / 2m+2m for control and 10f+10f / 10m+10m for LD, MD and HD **Phase II:** main study: 12 TK (PND 25 + 40): 2f+2f / 2m+2m for control and 10f+10f / 10m+10m for LD, MD and HD	oral / gavage **Phase I:** 0 – 3 – 10 – 30 **Phase II:** 0 – 1 – 3 – 10 1% carboxy methylcellulose + 0.5% Tween 80 in ultrapure water **Phase I:** PND 10 – 16 **Phase II:** PND 10 – 40	Mortality: **Phase I:** HD (30 mg/kg/d): 2 m + 1 f found dead between PND 14 and 15, 1 m euthanized in poor condition on PND 14. In addition 7 pups from HD TK group due to high mortality + clinical signs in HD group ➔ surviving HD animals euthanized on PND 16 **Phase II:** HD (10 mg/kg/d): 1 m euthanized in poor condition on PND 18, 1 f found dead on PND 15 due to early mortality + clinical signs in HD group ➔ dosing discontinued except for 10 HD TK rats / sex with last dose on PND 18 to allow blood collection for TK analysis Clinical signs: **Phase I:** HD: PND 13 onwards 5/6 m + 4/6 f with tremors, thin, cold to touch, ↓ activity, suspected dehydration, suspected empty stomach **Phase II:** PND 16, 17 and/or 18: abnormal gait, uncoordinated and/or locomotor stereotypy, tremors, limited usage of limbs, prostration, and/or ↓ activity Body weights (bw): **Phase I:**

		HD: -25% on PND 14 MD: -9 to -10% **Phase II:** HD: -12 to -18% on PND 17 MD: m: -6 to -10% from PND 14 to 41; f: -29% between PND 12 and 17 only, bw remains comparable to controls throughout postweaning period Clinical pathology (**Phase II rats only**): Haematology: MD (3 mg/kg/d) lymphocyte count ↓ 10% in m + f; MD (3 mg/kg/d) + LD (1 mg/kg/d) females only: ↓↓MCHC + ↑↑platelets MD (3 mg/kg/d) females only: ↑↑reticulocytes Clinical chemistry: MD (3 mg/kg/d): aspartate aminotransferase ↑↑ (m + f), alanine aminotransferase (↑↑m + ↑f), alkaline phosphatase (m + f), total bilirubin ↑↑f, phosphorus (↑↑m + f), cholesterin (↑↑f), calcium + potassium (↑↑f) compared to controls. ↑↑ phosphorus considered related to pharmacology of the compound LD (1 mg/kg/d) females only: ↑↑ cholesterin + calcium + phosphorus Histopathology (**Phase II rats only**): 3 mg/kg/d: In sections of heart of 2 males, mild or moderate mineralization in tunica media of proximal aorta near its origin (aortic root), characterized by multifocal dystrophic mineralization of medial smooth muscle cells; in the glandular stomachs of 6 males, minimal or mild mineralization multifocally within mucosa, characterized by oval to irregular, amphophilic deposits in upper to mid-level mucosa 10 mg/kg/d: In 3 males euthanized on day 16 PND, minimal to mild decreased cellularity (haematopoietic) in bone marrow (femur); relationship to test item administration considered equivocal due to low incidence + severity, + fact that maximum tolerated dose was exceeded, + absence of age matched control group

Co = control; LD = low dose group; MD = mid dose group; HD = high dose group; m = male; f = female; bw = body weight(s); fc = food consumption; ↓ = decrease(d); ↓↓ = significant decrease(d); ↑ = increase(d); ↑↑ = significant increase(d)

Local Tolerance

Gastric irritation in rats (Study AA30230)

The gastric irritation potential of binimetinib (10, 30, and 100 mg/kg, PO, single dose) in 1% CMC/ 0.5% Tween 80 in water was evaluated in male SD rats (N = 10 per group). No significant effects of binimetinib administration were observed at 10 and 30 mg/kg. At 100 mg/kg, binimetinib induced an increased incidence of superficial mucosal lesions (10/10 animals) and of hemorrhagic ulcers (9/10 animals) compared to vehicle-treated animals.

Skin irritation in rabbit (Study pcs-r502321)

The possible irritation or corrosion potential of a single dose of the test substance was assessed when administered to the intact skin of rabbits. Three rabbits were exposed to 0.5 grams of binimetinib, moistened with 0.4 mL water by application onto clipped skin for 4 hours using a semi-occlusive dressing. Skin reactions were assessed 1, 24, 48 and 72 hours after exposure. No skin irritation, corrosion or discoloration was caused by binimetinib.

Other toxicity studies

A study was conducted to evaluate the photosensitising potential of binimetinib after oral administration to female BALB/c mice. The study design and the major findings are outlined in Table 19.

Table 19: Local lymph node assay with exposure to UVA to evaluate the photosensitising potential of binimetinib

Study Type (Study ID) GLP	Species; Number/Dose/ Treatment Group	Dose (mg/kg/day) p.o.	Major findings*
Local lymph node assay (pcs-1170390) GLP (Ø skin bioanalysis) + toxicokinetics	Mouse Balb/c 6 females/dose / treatment group toxicokinetics: 9 females / dose group (+ toxicokinetic samples before sacrifice from all binimetinib treated animals and vehicle control)	0 (vehicle) - UVA 10 +/- UVA 30 +/- UVA 100 +/- UVA positive control: 100 mg/kg sparfloxacin +/- UVA dosing for 3 days	transient erythema of the tail and ear (MD,HD+UVA) significant increase in ear weight in binimetinib treated groups (MD +UVA, HD +/-UVA) increase in lymph node weight and cell count in irradiated group (HD +UVA) transient erythema or auricular lymph node hyperplasia in individual binimetinib treated mice plus irradiation **<u>positive control + UVA:</u>** statistically significant differences in ear weight, lymph node weight, lymph node cell count
NOAEL= 10 mg/kg/day (Cmax= 4.4 µg/mL, AUC_{0-24hr}= 16.0 µg.hr/mL) (*exposure at the NOAEL approximately 3.6-times the human clinical exposure)			

+ UVA: exposure to at least 10 J/cm^2 UVA light; *human exposure: AUC_{0-12hr}= 2.1 µg.hr/mL (Study CMEK162X2201; patients with 45 mg BID)

2.3.5. Ecotoxicity/environmental risk assessment

Table 20: Summary of main study results

Substance (INN/Invented Name):binimetinib			
CAS-number (if available): 606143-89-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	1.5 (pH 4 and 7) 2.1 (pH 9)	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	1.5 – 2.1	not B
Persistence	DT50 (12°C) of main transformation product M-1	294.5 /106.5	vP
Toxicity	NOEC		not T
PBT-statement :	The compound is not considered as PBT nor vPvB.		
Phase I			

Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	0.45	µg/L	> 0.01 threshold (Y)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 122.7 / 162.3 l kg^{-1} (sludge) K_{OC} = 709.3 / 1280.7 / 1477.4 l kg^{-1}(soil)	No soil assessment required
Ready Biodegradability Test	OECD 301	Not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	***System 1*** Parent: $DT_{50,\ water\ 20\ °C}$ = 6.2 d $DT_{50,\ sediment}$ = n.d. $DT_{50,\ whole\ system\ 20\ °C}$ = 7.1 d M-1: $DT_{50,whole\ system,\ 20\ °C}$ =138 d % shifting to sediment = 11.1 (day 14) NER = 52.8% (test end) TP >10%: M-1 max. 64% at d14 ***System 2*** Parent: $DT_{50,\ water\ 20\ °C}$ = 5.2 d $DT_{50,\ sediment}$ = n.d. $DT_{50,\ whole\ system\ 20\ °C}$ = 5.6 d M-1: $DT_{50,whole\ system,\ 20\ °C}$ = 49.9 d % shifting to sediment = 10.5 (day 14) NER = 66.1 % (test end) TP >10%: M-1 max. 75% at d28	Binimetinib is classified as very persistent (persistent transformation product M-1 DT_{50} = 295 d, normalized to 12°C)

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	NOEC	8400	µg/L	*Pseudokirchneriella subcapitata*
Daphnia magna. Reproduction Test	OECD 211	NOEC	650	µg/L	*Daphnia* magna
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	2200	µg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1000 000	µg/L	
Phase IIb Studies					
Sediment dwelling organism, *Chironomus riparius*	OECD 218	NOEC	20	mg/ kg	*Chironomus riparius*

2.3.6. Discussion on non-clinical aspects

In biochemical studies, binimetinib has been shown to be a potent and selective inhibitor of MEK1/2 with an enzyme IC50 of 12.1 nM.

In cellular studies in vitro, binimetinib potently inhibited MEK-dependent phosphorylation of ERK as well as B-Raf-mutant melanoma cell lines. In vivo, binimetinib significantly inhibited A375 xenograft tumours in nude mice as well as HMEX1906 a patient-derived xenografts a dose- and time-dependent

manner. Tumour inhibition was best achieved with the combination of either 10 or 30 mg/kg binimetinib and encorafenib.

In safety pharmacology studies, binimetinib did not have any adverse effects on cardiovascular (monkey telemetry), gastrointestinal motility and secretion (in rats), neurobehavioral (Irwin rats), renal (rats) or respiratory function (rats) up to the highest single dose tested (100 mg/kg in rats and 10 mg/kg in monkeys). These doses are above the MTDs determined in the repeat dose toxicity studies in rats and monkeys. In rats, no adverse effect on the main physiological functions were observed up to approximately 65-fold the human exposure at the therapeutic dose level. In monkeys, no cardiovascular effects were noted at about 1.2 to 1.6-fold the human exposure at the therapeutic dose, based on AUC.

The plasma protein binding has been measured at a range of physiologically relevant concentrations of 97.2%.

In vitro, binimetinib and its active metabolite (AR00426032) have no appreciable activity on hERG channel current (IC50 > 30 µM and > 100 µM, respectively).

Repeated oral administration of binimetinib in rats for up to 6 months was associated with soft tissue mineralisation, gastric mucosal lesions and reversible minimal to mild clinical pathology changes at 7 to 12.5 times human therapeutic exposures. Specifically, repeated administration of binimetinib to rats was associated with abrasion, alopecia and scabbing of the skin, and minimal to mild increases in neutrophils and monocytes, ALT, AST, urea and phosphorus, and decreases in calcium and albumin. Treatment related histopathological changes included cutaneous erosion/ulceration and multi-centric vascular and tissue mineralization, which only partially reversed after a treatment free period. Skin lesions were dose related in both severity and incidence and were only partially reversible. Dermatological reactions to the administration of binimetinib are a known clinical finding. The finding of mineralisation of soft tissues in the rat may be species specific and has been seen with another MAP kinase (MEK) inhibitor. The published literature confirms that MEK inhibition caused soft tissue mineralisation in the rat secondary to serum inorganic phosphorus increase, but nevertheless the molecular mechanisms remain unknown. In a gastric irritation study in rats, an increased incidence of superficial mucosal lesions and of hemorrhagic ulcers were observed. The observations were observed with greater frequency and at lower dose level in females than in males. In cynomolgus monkeys, oral administration of binimetinib was associated with gastro-intestinal intolerance, moderate clinical pathology changes, bone marrow hypercellularity and microscopic findings of gastrointestinal inflammation, reversible at the lowest doses which were below human therapeutic exposures.
Administration of binimetinib was also associated with weight loss, soft stools, decrease in red blood cell mass, increased platelet, monocyte and neutrophil counts, serum globulin, and decreases in serum albumin, and albumin/globulin ratio. All these changes were reversible after a treatment free period. Treatment-related histological findings included slight degeneration of the luminal epithelium and mixed cell infiltrates in the large intestine, mucosal hyperplasia in the cecum, colon and/or rectum.

Binimetinib was not genotoxic. The lack of studies on pharmacodynamics drug interactions, single dose toxicity, carcinogencity and reproduction toxicity are acceptable as per the ICH S9 guideline. (SmPC section 5.3).

Embryo-foetal development studies conducted in rats and rabbits showed evidence of embryotoxicity (increased post-implantation loss and resorptions) and teratogenicity in rabbits only (ventricular septal defects and pulmonary trunk alterations) (SmPC section 5.3). In rats, lower gestational body weight gain and fetal body weights and a decreased number of ossified fetal sternebrae were noted. No effects were noted at 14-times the human therapeutic exposure. In rabbits, mortality, maternal physical signs of toxicity, lower gestational body weight and abortion were noted. The number of viable foetuses and foetal body weights were reduced and post-implantation loss and resorptions were increased. An

increased litter incidence of foetal ventricular septal defects and pulmonary trunk alterations was noted at the highest doses. No effects were observed at 3times the human therapeutic exposure. No teratogenic effects were noted in rats and rabbits up to about 30- and 3-fold, respectively, the human exposure at the therapeutic dose, based on AUC. Therefore, studies in animals have shown reproductive toxicity (see section 5.3). There are no data from the use of binimetinb in pregnant women. Recommendations have been included in section 4.6 of the SmPC concerning pregnancy and that if binimetinib is used during pregnancy, or if the patient becomes pregnant while taking binimetinib, the patient should be informed of the potential hazard to the foetus. Women of childbearing potential must use effective contraception during treatment with binimetinib and for at least 1 month following the last dose.

Fertility studies were not conducted with binimetinib. In repeat-dose toxicity studies, no concern in terms of fertility was raised from pathological examination of reproductive organs in rats and monkeys. There are no data on the effect on fertility in humans for binimetinib.

Binimetinib has phototoxic potential *in vitro*.

A minimal risk for photosensitisation was shown *in vivo* at an oral dose providing 3.8-fold higher exposure than that achieved with the recommended dose in humans. These data indicate that there is minimal risk for phototoxicity with binimetinib at therapeutic doses in patients.

Binimetinib is neither expected to bio-accumulate, nor to show any significant transfer to sludge and soil. The environmental risk assessment indicates the proposed therapeutic use of binimetinib is not expected to pose a significant risk to the environment. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical studies (pharmacology, pharmacokinetics and toxicology), submitted for the marketing authorisation application for binimetinib, were considered adequate and acceptable for the assessment of non-clinical aspects. The lack of carcinogenicity, fertility and pre-and post-natal development studies were well justified. Relevant information on the non-clinical aspects of binimetinib has been included in section 4.6 and 5.3 of the product information. Binimetinib is not expected to pose a significant risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 21: Clinical pharmacology studies – Healthy volunteers

Study Code	Short Title	Design Number of subjects (n)	Formulation[1]	PK sampling[2]
ARRY-162-0601	Single ascending dose study to assess the safety, tolerability, PK and PD	Double-blind, placebo-controlled, dose-escalation (20)	Aqueous oral suspension	Rich
ARRY-162-0602	Multiple ascending dose study to assess the safety, tolerability, PK and PD	Double-blind, placebo-controlled, dose-escalation (38)	Aqueous oral suspension, PIC	Rich
CMEK162A2102	Single oral dose of 45 mg [^{14}C]-MEK162 study to investigate the absorption, distribution, metabolism, and excretion (ADME)	Open label, single dose (6)	Radio-labelled PIC	Rich

MEK162: binimetinib, PIC: powder-in-capsule.

[1] For detailed descriptions of clinical formulations and drug product please refer to Module 3.2.P.2.2; Pharmaceutical Development.

[2] > 6 samples per 24-hour period=Rich.

Table 22: Study overview of single agent binimetinib clinical pharmacology studies in cancer patients

Study Code	Study Title	Number of subjects (n)	Formulation	PK sampling[1]
ARRAY-162-111	A Phase 1 dose-escalation study of oral ARRAY-438162 in patients with advanced solid tumors followed by expansion cohorts in patients with advanced or metastatic biliary cancer or metastatic colorectal cancer	93	Tablet (ACSF, EPT, QS-CSF)	Rich/Sparse
CMEK162X1101	A Phase 1 study of oral binimetinib in Japanese patients with advanced solid tumors (enrolment complete)	21	Tablet (P3-MI, ACSF)	Rich
CMEK162X2201	A Phase 2 open-label study of single-agent binimetinib in adult patients with advanced cutaneous malignant melanoma, harboring *BRAF* V600 or *NRAS* mutations (enrolment complete)	183	Tablet (ACSF)	Rich
CMEK162A2301	The NEMO trial (*NRAS* melanoma and MEK inhibitor): A randomized Phase 3, open-label, multicenter, 2-arm study comparing the efficacy of binimetinib versus dacarbazine in patients with advanced unresectable or metastatic *NRAS* mutation-positive melanoma	402	Tablet (P3-MI)	Sparse

ACSF: Array clinical service formulation, EPT: early prototype tablet, QS-CSF: QS Pharma clinical service formulation, P3-MI: Phase 3-market image.

[1] > 6 samples per 24-hour period=Rich; ≤ 5 samples per 24-hour period=Sparse.

Table 23: Studies of binimetinib in combination with encorafenib in cancer patients

Study Code	Study Title	Number of subjects	Binimetinib Formulation	PK sampling[1]
CMEK162X2110	A phase Ib/II, multicenter, open-label, dose escalation study of LGX818 in combination with MEK162 in adult patients with *BRAF* V600-dependent advanced solid tumors	126	Tablet (P3-MI)	Rich
CLGX818X2109 (Part 1 only)	The LOGIC 2 trial A phase II, multi-center, open-label study of sequential LGX818/MEK162 combination followed by a rational combination with targeted agents after progression, to overcome resistance in adult patients with locally advanced or metastatic *BRAF* V600 melanoma	158 (Part 1)	Tablet (P3-MI)	Sparse (Part 1)
CMEK162B2301 (Part 1 only)	COLUMBUS – Combined LGX818 used with MEK162 in *BRAF* mutant unresectable Skin cancer: 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	577	Tablet (P3-MI)	Sparse

P3-MI: Phase 3-market image.
[1] > 6 samples per 24-hour period=Rich; ≤ 5 samples per 24-hour period=Sparse.

2.4.2. Pharmacokinetics

Binimetinib has been studied in a number of clinical studies to determine the PK in healthy volunteers and patients. A population PK analysis was also performed to determine important covariates on the PK and to support an analysis of exposure versus efficacy and safety.

Absorption

Study MEK162A2103: A randomized, single-centre, open-label, three-period, cross-over study to investigate the effect of food on the pharmacokinetics of oral MEK162 in healthy subjects

Study MEKA62A2103 investigated the effect of food on the bioavailability of binimetinib. The study was an open-label, randomized, 3-treatment, 3-period, six-sequence, crossover study evaluating the effect of food on the bioavailability of binimetinib tablets (P3-MI) in healthy subjects. Subjects were randomized to 1 of 6 treatment sequences. Subjects received the following treatments in a crossover manner at the same time of the day in each period of the study.

Treatment 1 consisted of single oral 45 mg dose (3 x 15 mg tablets) of binimetinib with a high-calorie HFM (Test 1). Treatment 2 consisted of single oral 45 mg dose (3 x 15 mg tablets) of binimetinib with a low-calorie LFM (Test 2). Treatment 3 consisted of single oral 45 mg dose (3 x 15 mg tablets) of binimetinib in FS (reference), where subjects fasted for at least 10 hours prior to dosing and 4 hours after dosing.

Meal composition for a representative LFM consisted of approximately 334 kcal, of which approximately 23% of the caloric content was attributed to fat.

A summary of the key PK parameters from study MEK162A2103 is presented in Table 24.

Table 24: Summary of the Pharmacokinetic Parameters of binimetinib in plasma following administration of Binimetinib (P3-MI) to health subjects under fasted conditions and with high and low-fat meal

Treatment[a]	Statistic	AUC_{inf} (ng*hr/mL)	C_{max} (ng/mL)	T_{max} (h)
Fasted State	n	12	12	12
	Geo-mean	2220	452	-
	Geo-CV (%)	34.1	47.9	-
	Median	-	-	0.875
	[Min; Max]	-	-	[0.500; 4.00]
Low Fat Meal	n	12	12	12
	Geo-mean	2220	584	-
	Geo-CV (%)	22.7	21.1	-
	Median	-	-	1.25
	[Min; Max]	-	-	[0.500; 2.00]
High Fat Meal	n	12	12	12
	Geo-mean	2200	374	-
	Geo-CV (%)	31.5	23.9	-
	Median	-	-	2.03
	[Min; Max]	-	-	[0.750; 4.02]

Source: [Study MEK162A2103 CSR, Table 11-3]
Key: AUC_{inf}: area under the curve to infinity, C_{max}: maximum observed plasma concentration, CSR: clinical study report, Geo-CV: geometric coefficient of variation, Geo-mean: geometric mean, Max: maximum observed value, Min: Minimum observed value; n: number of subjects with non-missing values, P3-MI: phase 3-market image, T_{max}: time to maximum observed plasma concentration.
[a] P3-MI was administered as a single oral 45 mg dose of binimetinib (3 x 15 mg tablets).

Distribution

Plasma binimetinib concentrations exhibit biphasic elimination with a median terminal half-life of 4–13 hours across all healthy subject and patient studies. The apparent oral clearance was 28.2 L/h and apparent volume of distribution based on the human ADME study was about 384 L.

Elimination

CMEK162A2102: A Phase I, Single Centre, Open-Label Study to Investigate the Absorption, Distribution, Metabolism, and Excretion (ADME) Of MEK162 Following a Single Oral Dose of 45 mg [^{14}C] MEK162 in Healthy Male Subjects

The clinical study CMEK162A2102 was conducted in healthy subjects with an objective to determine the rates and routes of excretion of binimetinib and its metabolites, including mass balance of total drug related radioactivity in urine and faeces, following the administration of a single 45 mg dose of [^{14}C] binimetinib.

After the oral administration of binimetinib to humans, an average of 62.3% of the administered radioactive dose was excreted in the faeces and included a total of six identified metabolites and binimetinib. Binimetinib was the most abundant radioactive component and accounted for 21.1% to 45.7% of the administered radioactive dose, with an average value of 29.8%. The most abundant metabolites were M4, an ethane-diol cleavage product, and M15.9, carboxylic acid formed from amide hydrolysis, accounting for 17.2% and 6.7% of the dose, respectively. All other metabolites were present at ≤ 2.7% of the dose.

Overall, a mean of 31.4% of the radioactivity dose was eliminated in the urine. A total of 14 metabolites and binimetinib were identified. Binimetinib was the most abundant radioactive component

and accounted for 5.3% to 8.1% of the administered radioactive dose, with an average value of 6.5%. The most abundant metabolites were M10.9 (direct glucuronide of binimetinib), M3 (AR00426032, N-demethylated binimetinib), and M10.2 (another direct glucuronide of binimetinib), accounting for 6.2%, 5.1% and 4.2% of the dose, respectively. All other metabolites were present at ≤ 3.2% of the dose. The mean cumulative excretion of radioactivity in urine and faeces is shown in Figure 3.

The estimated mean CLR value of 1.78 L/hr accounted for 6.3% of the total mean CL/F value of 28.2 L/hr.

Table 25: Amounts of Binimetinib and its metabolites in faeces following a single oral dose of 45 mg of 14C-Binimetinib

Metabolite\Subject	5010-00006	5010-00020	5010-00028	5010-00034	5010-00037	5010-00039	Mean	SD
P22.9	1.5	1.2	1.6	2.1	1.6	2.3	1.7	0.4
M24.1	2.5	0.7	1.5	3.6	0.4	0.5	1.6	1.3
M3 (AR00426032)	5.9	2.1	4.9	1.7	0.5	0.6	2.6	2.3
M15.9	5.9	5.0	5.5	9.0	6.7	8.1	6.7	1.6
binimetinib	35.7	21.1	45.7	31.0	23.8	21.2	29.8	9.7
M17.0	1.5	5.2	0.8	3.2	3.8	1.9	2.7	1.6
M4	4.5	27.8	4.8	18.6	24.4	23.2	17.2	10.2

Note: Amounts expressed as % of dose

In the human ADME study (CMEK162A2102), approximately 60% of the plasma radioactivity AUC was attributable to binimetinib.

An *in vitro* study using human hepatocytes was conducted to assess the relative contributions of CYP and UGT enzymes to binimetinib metabolism. The metabolic clearance of binimetinib is likely to be dominated by the glucuronidation pathway. The relative contributions of the glucuronidation, hydrolysis, or the oxidative pathways (AR00426032 or M3) to overall binimetinib metabolism in human hepatocytes were 45.1%, 5.1% and 2.4%, respectively. In this study, unchanged binimetinib accounted for 17.3% of total radioactivity after 24 hours.

The primary metabolic pathways include glucuronidation (up to 61.2% via UGT1A1 per *in vitro* data) and N-dealkylation, amide hydrolysis (up to 17.8% via CYP1A1 and CYP2C19 based on *in vitro* data), respectively. The estimated mean CLR value of 1.78 L/hours was 6.3% of the total mean CL/F value of 28.2 L/hr.

Dose proportionality and time dependencies

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

In study ARRY-162-0601, healthy subjects received single, escalating doses of 5, 10, 20, 30 and 40 mg binimetinib as an oral suspension. The geometric mean of binimetinib exposure parameters (Cmax and Area Under the Concentration Time curve [AUC]) generally increased with increasing dose and inter-subject variability [intra-cohort % Coefficient of Variation (CV)] ranged from 9.95% to 53.5%. The median Apparent Terminal Half-Life (t1/2) of binimetinib across doses was 5.98 hours, and the median Time to Maximum Observed Plasma Concentration (Tmax) was 1 hour post-dose. The overall Geometric Mean Ratio (GMR) of AR00426032 to binimetinib exposure, metabolic ratio of parent drug

AUC and metabolite AUC (Mean Ratio of Exposure [MRAUC]) was 12.8%. The overall mean percent of the dose excreted into urine over a 24-hour period as unchanged binimetinib and AR00426032 was 2.5% and 4.4%, respectively.

The PK of binimetinib and AR00426032 after repeat doses are studied in four clinical studies (ARRY-162-0602, ARRAY-162-111, CMEK162X2201 and CMEK162X1101) and are summarized in Table 26 and Table 27 respectively.

Table 26: Pharmacokinetics of Binimetinib following Multiple Doses

Study Code/Dose and Regimen (n)	Pharmacokinetic Parameter on Day 14 or 15*							
	C_{max}[b] ng/mL	T_{max}[c] hr	$AUC_{0,\tau}$[b] ng/mL*hr	$AUC_{0,12}$[b] ng/mL*hr	R_{acc}[b,d]	LFAUC[b,d]	CL/F[b] L/hr	Vz/F[b] (L)
ARRY-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)
20 mg 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								
30 mg 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
60 mg BID (7)	512 (30.8)	3.00 (0.53 - 7.12)	1820 (14.4)	ND	1.17 (18.4)	NC	NC	NC
60 mg BID (7) (Expansion Phase)	594 (68.8)	1.50 (1.00 - 7.02)	3760 (NC)	ND	2.50 (NC)	NC	NC	NC
CMEK162X1101								
30 mg 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
60 mg 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

Key: AUC: area under the concentration time curve, BID: twice daily, CL/F: apparent total clearance following oral administration, C_{max}: maximum observed plasma concentration, n: Number, NC: not calculable, ND: not determined, LFAUC: left ventricular area under the curve, QD: once daily, R_{acc}: accumulation ratio, T_{max}: time to maximum observed plasma concentration, Vz/F: terminal volume of distribution.

* ARRY-162-0602 = Day 14, ARRAY-162-111, CMEK162X1101 and CMEK162X2201 = Day 15.

[b] Geometric mean (Coefficient of Variation %).

[c] Median (minimum-maximum).

[d] ARRAY-162-111 = $AUC_{0,\tau}$, CMEK162X1101 and CMEK162X2201 = AUC_{0-12}.

Table 27: Pharmacokinetics of AR004260322 Following Multiple doses

Study Code/ Dose and Regimen (n)	Pharmacokinetic Parameter on Day 14 or 15*				
	C_{max}[b] ng/mL	T_{max}[c] hr	AUC_{0-8}[b] ng/mL*hr	AUC_{0-12}[b] ng/mL*hr	R_{acc}[b,d]
ARRY-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
20 mg 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					
30 mg 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)
60 mg BID (7)	27.8 (101)	2.00 (1.00 - 7.12)	137 (60.4)	ND	0.869 (31.3)
60 mg BID (7) (Expansion Phase)	15.2 (111)	2.00 (0 - 3.00)	349 (NC)	ND	1.05 (NC)
CMEK162X1101					
30 mg 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
60 mg BID (20)	25.5 (124)	1.50 (0.00 - 8.00)	ND	322 (NC)	1.02 (NC)

Key: AUC: area under the concentration time curve, BID: twice daily, C_{max}: maximum observed plasma concentration, n: number, NC: not calculable, ND: not determined, QD: once daily, R_{acc}: accumulation ratio, T_{max}: time to maximum observed plasma concentration, Vz/F: terminal volume of distribution.

[a] ARRY-162-0602 = Day 14, ARRAY-162-111, CMEK162X1101 and CMEK162X2201 = Day 15.

[b] Geometric mean (Coefficient of Variation %).

[c] Median (minimum-maximum).

[d] ARRAY-162-111 = AUC_{0-8}, CMEK162X1101 and CMEK162X2201 = AUC_{0-12}.

Pharmacokinetics in target population

Table 28: Binimetinib Pharmacokinetic Parameters on Cycle 1 Day 15

Study Code, Dose and Regimen (n)	$C_{max,ss}$ (ng/mL)	T_{max} (h)	$AUC_{tau,ss}$ (ng.h/mL)	R_{AUC}	CL/F (L/h)	V_z/F (L)
Study ARRAY-162-111 Binimetinib Single Agent						
45 mg Binimetinib BID (N=4)	273 (64.7)	2.00 (1.07, 2.87)	ND	1.50 (NC)	NC	NC
Study CMEK162X2201 Binimetinib Single Agent						
45 mg Binimetinib BID (N=22)	438.5 (53.9)	1.48 (0.42, 8.00)	2103 (38.4)	1.31 (NC)	20.2 (24.1)	NC
Study CMEK162X2110 45 mg Binimetinib BID in Combination with Escalating Doses of Encorafenib						
50 mg Encorafenib QD (N=6)	648 (40.9)	1.50 (0.500, 2.50)	2690 (50.0)	1.50 (16.8)	16.8 (50.1)	111 (119.0)
100 mg Encorafenib QD (N=5)	526 (48.9)	1.50 (0.500, 1.62)	2480 (37.7)	1.25 (12.3)	17.8 (33.4)	126 (70.5)
200 mg Encorafenib QD (N=4)	532 (92.0)	2.01 (1.52, 2.50)	2300 (92.2)	1.06 (13.4)	19.6 (91.8)	53.5 (NC)
400 mg Encorafenib QD (N=5)	464 (84.9)	1.50 (1.48, 1.67)	1880 (59.0)	0.938 (40.1)	23.9 (59.0)	138 (63.6)
450 mg Encorafenib QD (N=13)	595 (39.0)	1.57 (0.483, 2.57)	2420 (33.9)	0.987 (32.0)	18.5 (33.2)	91.8 (45.0)
600 mg Encorafenib QD (N=8)	651 (52.1)	1.48 (0.500, 2.68)	2210 (67.9)	0.928 (34.4)	25.2 (37.7)	NC (NC)
800 mg Encorafenib QD (N=6)	705 (27.5)	2.13 (0.533, 2.50)	2500 (20.2)	1.13 (36.7)	18.0 (25.6)	68.8 (25.2)

Geometric mean (CV% geometric mean) values were reported for the parameters, except for T_{max} for which median (min, max) were shown.
R_{AUC}=AUC_{0-8h} in ARRAY-162-111 and AUC_{0-12h} in CMEK162X2201.
NC: not calculated; ND: not determined.

Special populations

Impaired renal function

ARRY-162-106: A Phase 1, Open-Label, Multicentre, Single-Dose Study to Evaluate the Pharmacokinetics of Binimetinib in Healthy Subjects with Normal Renal Function and Subjects with Impaired Renal Function

The impact of renal impairment (as determined using the modification of diet in renal disease formula) on 45 mg single dose binimetinib as monotherapy was assessed in a clinical study with an abbreviated design (Study ARRAY-162-106). Results from the severe impairment cohort (i.e. subjects with eGFR ≤29 mL/min/1.73 m2, N=6) indicated an approximate 29% and 21% increase in binimetinib exposure (AUCinf) and in Cmax, respectively, compared with matching healthy subjects (N=6). This increase in exposure was within the variability observed in both cohorts (25.6% and 38.2% for AUC and 42.5% and 48.7% for Cmax). Compared with the healthy subjects, the severe renal impairment cohort exhibited a 22% lower clearance and a slightly longer t1/2 (11.2 vs 9.16 hours).

In the binimetinib and encorafenib combination model, moderate and severe renal impairment was assessed as a categorical covariate using eGFR for assessment. A 5% increase in CL/F was observed in the moderate/severe group (grouped because of limited number of severe patients). In addition, a 2% increase in CL/F was observed in the mild impairment group.

Impaired hepatic function

CMEK162A2104: A Phase 1, Multicentre, Open-Label, Single-Dose Study to Assess the Pharmacokinetics of MEK162 in Subjects with Mild, Moderate and Severe Hepatic Impairment

Study CMEK162A2104 was a dedicated clinical study investigating the binimetinib PK as monotherapy in subjects with hepatic impairment, as defined by the NCI Organ Dysfunction Working Group versus healthy subjects. Healthy subjects were enrolled based on matched age, gender and body weight to subjects with hepatic impairment and could have matched more than one subject. Six subjects with mild hepatic impairment, 6 subjects with moderate impairment, 5 subjects with severe hepatic impairment and 7 matching healthy subjects have been dosed.

For the mild impairment versus healthy subject comparison, GMR (90% CI) for AUC0-inf and Cmax were 1.10 (0.86, 1.40) and 1.11 (0.79, 1.57), respectively. For the moderate impairment (i.e. total bilirubin levels >1.5 and ≤3.0 × ULN and any AST value) versus healthy subject comparison, GMR (90% CI) for AUC0-inf and Cmax were 1.94 (1.53, 2.47) and 1.38 (0.98, 1.95), respectively. Due to the 2-fold increase in exposure observed in the moderate impairment cohort, the dose was reduced to 15 mg in the severe impairment cohort. For the severe impairment (i.e. total bilirubin levels >3.0 × ULN and any AST value) versus healthy subject comparison, GMR (90% CI) for AUC0-inf and Cmax were 2.11 (1.62, 2.74) and 1.57 (1.12, 2.20), respectively.

Population Pharmacokinetic and Exposure Response Analysis of Binimetinib

The study CP16-001 was conducted with the objective to develop a PopPK model for binimetinib and active metabolite AR00426032, to predict binimetinib and active metabolite exposures.

Final population PK models were used to derive rich concentration-time profiles and exposure parameters were derived according to the randomized dose in patients enrolled in all studies. Simulations were derived based on steady-state conditions. Exposure parameters of binimetinib following concomitant administration with encorafenib in patients enrolled in the COLUMBUS Part 1 study are presented in Table 29.

Table 29: Exposure parameters of Binimetinib Administered in combination with Encorafenib (COLUMBUS Study, Part 1)

Statistics	Combo (Binimetinib at 45 mg and Encorafenib at 450 mg) (n=192)				
	AUCss (µg.h/mL)	Cminss (ng/mL)	Cmaxss (ng/mL)	T_{max} (h)	$t_{1/2\beta}$ (h)
Mean (CV%)	2.28 (23.8%)	38.3 (33.1%)	692 (32.1%)	1.22 (69.0%)	17.8 (11.6%)
[Min, Q25]	[1.15, 1.90]	[13.1, 28.6]	[191, 541]	[0.509, 0.809]	[4.81, 16.7]
[Q25, Median]	[1.90, 2.23]	[28.6, 36.0]	[541, 677]	[0.809, 1.01]	[16.7, 17.7]
[Median, Q75]	[2.23, 2.54]	[36.0, 44.2]	[677, 813]	[1.01, 1.31]	[17.7, 19.1]
[Q75, Max]	[2.54, 4.18]	[44.2.9, 89.5]	[813, 1610]	[1.31, 6.31]	[19.1, 23.5]

AUCss= Area-under the curve under steady-state over the dosing interval; Cmax= Maximum concentration at steady-state; Cmin= Minimum concentration at steady-state; CV= Coefficient of variation; Max= Maximum; Min= Minimum; n= Number of subjects; Q25= 25th percentile; Q75= 75th percentile; Tmax= Time to reach maximum concentration; $t_{1/2\beta}$= Terminal elimination half-life

Gender

In the binimetinib monotherapy analysis, female subjects (N=387) were found in a greater proportion in the population PK analysis dataset than males (N=214). A similar trend was observed for binimetinib in the binimetinib and encorafenib combination population model including 166 females and 256 males, with females exhibiting a 13% lower CL/F and 14% lower V/F relative to males.

Race

Japanese patients have shown 1.5 to 2-fold higher binimetinib exposures (Cmin,ss, Cmax, AUC0-12h) than non-Japanese patients after administration as monotherapy. In Study CMEK162X1101, Japanese patients (N=9) were shown to have higher steady-state binimetinib exposures compared to all patients in Study CMEK162X2201 (N=22) following administration of 45 mg binimetinib. The mean Cmax and AUC0-12h values were 771 ng/mL versus 439 ng/mL and 3550 ng.h/mL versus 2103 ng.h/mL, respectively. In Study CMEK162A2301, plasma concentrations of binimetinib and AR00426032 were analysed in Japanese versus non-Japanese patients. Six Japanese patients were identified in the binimetinib arm for comparison to non-Japanese patients. At steady-state condition (i.e. pre-dose Week 4), Japanese patients showed higher mean binimetinib concentrations than non-Japanese patients (305 ng/mL versus 127 ng/mL pre-dose, respectively).

Weight

For an individual in the 95th percentile of weight (i.e. 110 kg), the population PK analysis suggested a 26% change in V/F compared to the typical individual of 78 kg, and a 23% change for an individual in the 5th percentile of weight (53kg). A similar trend between body weight and binimetinib V/F was observed in the binimetinib and encorafenib combination model with 34% increase at the 95th percentile (i.e. 112 kg) and 26% decrease at the 5th percentile (i.e. 54 kg).

Elderly

Bayesian PK parameters for binimetinib were derived and summarised according to the proposed age categories and descriptive statistics are provided in each age group in the tables below.

Table 30: Bayesian PK Parameters by age categories

65-74 years

STUDY	Patient ID	Ka (1/h)	V/F (L)	V2/F (L)	Cl/F (L/h)	Cl2/F (L/h)	Tlag (h)	AGE (y)
Mean		2.86	99.1	215	18.5	14.3	0.164	69.2
SD		1.99	24.5	172	7.00	1.63	0.00	2.83
CV%		69.5	24.7	80.0	37.9	11.4	0.00	4.09
Min		0.151	46.9	57.1	7.19	10.1	0.164	65.0
Max		9.31	190	1782	64.4	19.8	0.164	74.0
Median		2.51	98.9	186	17.5	14.2	0.164	69.0
N		146	146	146	146	146	146	146

Cl/F: apparent clearance; Cl2/F: apparent inter-compartmental clearance; Ka: first order absorption rate constant; Tlag: lag time; V/F: apparent central volume of distribution; V2/F: apparent peripheral volume of distribution

Source: CP16-001 report appendix 8.1.7

75- 84 years

STUDY	Patient ID	Ka (1/h)	V/F (L)	V2/F (L)	Cl/F (L/h)	Cl2/F (L/h)	Tlag (h)	AGE (y)
Mean		3.00	86.3	198	15.3	14.1	0.164	78.8
SD		2.32	19.7	97.8	5.87	1.71	0.00	2.56
CV%		77.5	22.8	49.4	38.4	12.2	0.00	3.25
Min		0.0626	46.3	65.9	6.86	10.0	0.164	75.0
Max		14.1	139	799	41.9	18.6	0.164	84.0
Median		2.74	84.5	184	14.5	14.1	0.164	79.0
N		64	64	64	64	64	64	64

Cl/F: apparent clearance; Cl2/F: apparent inter-compartmental clearance; Ka: first order absorption rate constant; Tlag: lag time; V/F: apparent central volume of distribution; V2/F: apparent peripheral volume of distribution

Source: CP16-001 report appendix 8.1.7

85 years and over

STUDY	Patient ID	Ka (1/h)	V/F (L)	V2/F (L)	Cl/F (L/h)	Cl2/F (L/h)	Tlag (h)	AGE (y)
Mean		2.77	95.4	183	14.5	13.3	0.164	87.0
SD		1.31	18.4	11.9	2.03	1.24	0.00	2.08
CV%		47.2	19.3	6.53	14.0	9.35	0.00	2.39
Min		0.919	70.3	163	11.4	12.0	0.164	85.0
Max		4.39	120	196	16.5	15.2	0.164	90.0
Median		2.98	93.3	180	15.3	12.9	0.164	87.0
N		7	7	7	7	7	7	7

Cl/F: apparent clearance; Cl2/F: apparent inter-compartmental clearance; Ka: first order absorption rate constant; Tlag: lag time; V/F: apparent central volume of distribution; V2/F: apparent peripheral volume of distribution

Source: CP16-001 report appendix 8.1.7

Table 31: Number of elderly subjects for PK studies

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials	201/749	70/749	n/a

Pharmacokinetic interaction studies

Binimetinib showed weak inhibition (IC50 ~ 50 µM) of CYP1A2 and CYP2C9. Very little or no inhibition of CYP2A6, CYP2C8, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 was observed at binimetinib concentrations of up to 100 µM. Binimetinib showed no apparent time-dependent inhibition of CYP1A2, CYP2C9, CYP2D6 or CYP3A4/5 at binimetinib concentrations of up to 50 µM.

Binimetinib showed inhibition of CYP2B6 with an IC50 value of ~6 µM and a Ki value of 1.7 µM. A basic model for reversible inhibition was used to calculate the R value of inhibition of CYP2B6 with binimetinib using the parameters obtained in the *in vitro* studies. Since the R value was 1.61, the static mechanistic model was used to calculate the AUCR to determine if an *in vivo* study was warranted (if AUCR > 1.25). The AUCR was calculated to be 1.03, therefore it was concluded that binimetinib was not likely to be an inhibitor of CYP2B6 and an *in vivo* study not needed to assess the interaction potential.

Binimetinib showed a 1.88 to 2.24-fold induction for CYP2C9 mRNA with 20 µM of binimetinib, relative to the vehicle control in primary human hepatocytes. The induction at lower concentrations (0.1, 1, and 10 µM) was less than 2-fold. Treatment of hepatocytes with binimetinib caused no induction of CYP2C9 activity, as shown by less than 2-fold metabolism of diclofenac. In the second experiment, binimetinib concentrations ranged from 0.01 to 30 µM, and a 2.68-fold induction was observed only in one of the two hepatocyte donors at 30 µM.

CYP3A4 induction was observed at all concentration ranges tested. At 0.1 µM binimetinib the induction ranged from 1.88 to 3.00-fold, and at 20 µM binimetinib, the induction ranged from 23.7 to 37.2-fold.

Binimetinib was a weak inhibitor of UGT1A-mediated glucuronidation of SN-38 with an IC50 value of greater than 25 µM. The average percent of inhibition at 25 µM was 20.3%. The effect of binimetinib on UGT1A enzyme activities is presented in Table 32.

Table 32: Effect of Binimetinib on UGT1A Enzyme Activities

UGT Isoform	Substrate	Average[a] binimetinib IC_{50} (µM)	% Inhibition of binimetinib at 25 µM	Saquinavir (Control Compound) IC_{50} (µM)
UGT1A	SN-38	> 25	20.3	5.84

Key: UGT: uridine diphosphate glucuronosyltransferase, UGT1A : uridine diphosphate glucuronosyltransferase 1A
[a] Average taken from duplicate IC_{50} values.

Binimetinib was not found to be an *in vitro* inhibitor of BCRP or P-gp. BCRP and P-gp efflux activity were largely unaffected by concentrations of binimetinib up to 50 µM.

Study ARRAY-162-105 was a study in 15 healthy subjects investigating the PK of binimetinib in the presence of the proton-pump inhibitor rabeprazole. The GMR for Area Under the Concentration-Time Curve from Time 0 Extrapolated to Infinity (AUCinf) increased 4% (GMR = 1.04) following co-administration with rabeprazole. The treatment groups were bioequivalent as indicated by the 90% CI of the GMR (0.930 – 1.17). Likewise, there was no effect on Tmax. In contrast, Cmax was decreased after administration with rabeprazole by 17% (GMR = 0.826) and this change was determined to be statistically significant as indicated by the 90% CI of the GMR (0.692 – 0.984). However, the magnitude of change (17%) was less than the reported variability in the study for Cmax across both treatment periods (30.9 % to 41.7%).

Pharmacokinetics using human biomaterials

In humans, the mean plasma protein binding of binimetinib was 97.4% when evaluated by the rapid equilibrium dialysis method (DMPK R1300621_DMPK R1300621a). The blood-to-plasma concentration ratios of binimetinib ranged from 0.65 to 0.99 in the species tested, and appeared to be independent of concentration. In humans, the blood-to-plasma ratio was 0.72 over the concentration range evaluated (50 to 10,000 ng/mL).

Characterization of Binimetinib as a Substrate of Xenobiotic Transporters

In Caco-2 cells, MEK162 was confirmed as an efflux substrate (BA/AB >2.0), since, in the presence of verapamil, a specific P-gp inhibitor, the transwell permeability and efflux of binimetinib were increased and reduced, respectively. Binimetinib was confirmed as a substrate of both P-gp and BCRP in MDR1-expressing LLC-PK1 cells and BCRP expressing MDCK cells, respectively.

The potential involvement of several uptake transporter families (OCT1, OATP1B1, OATP1B3, and OATP2B1) in binimetinib plasma clearance was investigated using a representative cocktail of transporter inhibitors in human hepatocyte assays (DMPK R1100398). The data suggested that hepatic uptake transporters are not involved in binimetinb plasma clearance and distribution into human hepatocytes. Additionally, binimetinib does not display significant active renal secretion as only 6.5% of the dose was excreted in urine as binimetinib in humans (Study CMEK162A2102); as such it was not evaluated as a substrate of OAT1/3 and OCT2.

Transporter Inhibition
Binimetinib was not found to be an inhibitor of BCRP or P-gp. BCRP and P-gp efflux activity were largely unaffected by concentrations of binimetinib up to 50 µM (DMPK R 1100165). MEK162 did not affect the P-gp mediated transport of digoxin in Caco-2 or MDR1 transfected LLC-PK1 cell monolayers (DM05-042-A1_DM05-042-A2).

Binimetinib was shown to reduce [3H] estradiol 17ß-glucuronide ([3H]E217ßG) accumulation into OATP1B1 and OATP1B3-expressing cells in a dose-dependent manner, however, the estimated IC50 values for inhibition of OATP1B1 or OATP1B3-mediated ([3H]E217ßG) uptake by binimetinib were 23.6 ± 9.6 µM and ~29 µM, respectively. Binimetinib did not inhibit the transport activity of OCT1 (1 to 100 µM) but was a weak inhibitor of the transport activity of OCT2 (IC50 18.1 ± 1.3 µM) in vitro). The IC50 values for binimetinib inhibition of OAT1 and OAT3 activities were approximately 27 µM and 1.9 ± 0.17 µM, respectively. Additionally, binimetinib was assessed as an inhibitor of BSEP-mediated taurocholic acid transport in inside-out membrane vesicles containing expressed BSEP from 0.1 to 25 µM. Binimetinib did not cause a dose-dependent inhibition of BSEP activity (~20% maximal inhibition). Likewise, binimetinib is not predicted to affect transport of substrates of the renal MATE1 or MATE2-K transporters. Binimetinib was not a potent inhibitor of metformin uptake by MATE1 (IC50 >50 µM) and did not inhibit MATE2-K when tested up to 50 µM in recombinant HEK cell lines expressing each transporter (DMPK R 1100433; DMPK R 1200819; DMPK R 1200760; DMPK R 1400791; DMPK R 1400790).

2.4.3. Pharmacodynamics

Mechanism of action

See non-clinical pharmacology.

Primary and Secondary pharmacology

In Study ARRAY-162-111, post-dose decreases in tumour necrosis factor alpha (TNFα) levels were observed in serum samples, as well as post-dose decreases in Ki67 and phosphorylated ERK (pERK) levels in skin punch biopsies for patients in the 30 to 60 mg BID dose cohorts.

In Study CMEK162X1101, skin expression of pERK was evaluated as potential surrogate PD marker of binimetinib inhibition, pre-dose at baseline and post-dose on Day 15 of Cycle 1. Tumour tissue was not evaluated as no paired tumour sample was available. A total of 11 out of 17 patients with matched skin samples demonstrated a decrease in pERK H-score from baseline (4 of 6 patients in the 30 mg BID and 7 of 11 patients in the 45 mg BID dose level cohorts). The median (range) percentage change from baseline to Day 15 of Cycle 1 was −34.6% (−95.3% to 108.3%), indicating inhibition of the target at both evaluated dose levels.

Exposure-Safety

Exposure-safety analyses were conducted using a logistic regression model across multiple oncology studies with binimetinib in combination with encorafenib (Studies CMEK162B2301 [Part 1], CMEK162X2109, CMEK162X2110 and CLGX818X2101). The relationships between model-predicted binimetinib and encorafenib exposure (AUCss) and the expected incidence of increased ALT, PPE, pyrexia and diarrhoea were assessed. Exposure-response relationships for binimetinib and encorafenib in combination were similar in most instances due to the confounding effect of the combination therapy.

When anchored for encorafenib monotherapy, high AUCss of binimetinib were associated with slightly higher probabilities of increased ALT (all grades), pyrexia (grade ≥2) and diarrhoea (grade ≥2), though none were statistically significant.

Binimetinib appeared to mitigate the effect of encorafenib on PPE (grade ≥2) by reducing the probability from 32.4% to 42.6% across quartiles of encorafenib exposure to 1.0% to 2.0%.

Logistic regression evaluation of grade 2 or greater LVEF reduction and exposure found no significant relationships for increased incidence and increased exposure for model predicted exposure metrics (Cmin,ss, AUCtau,ss, Cmax,ss [p > 0.05]). Additional ER analyses were conducted on CHMP request including the ADRs skin rash (grade≥2), skin infections (grade≥2), skin neoplasms (grade≥2), retinal events (grade≥2), high levels of AST (all grades), high levels of gGT (all grades), CK elevations (all grades) and arthralgia (grade≥2) and included patients from COLUMBUS parts 1 and 2.

Results from the updated logistic models with positive relationship (i.e. harmful effect [p<0.05]) between the exposure and the probability of adverse events showed that all higher exposure parameters levels of binimetinib (Cmin,ss, Cmax,ss, AUCtau,ss) were associated with increased probabilities of retinal events (grade ≥ 2), high levels of AST (all grades) and high levels of CK (all grades).

For the probability of high CK levels, the probability estimated with the absence of binimetinib (i.e., encorafenib monotherapy) was 3.84% and then this probability increased to 11.73%, 15.95%, 20.03% and 30.08% for patients with AUCss binimetinib in the 1st, 2nd, 3rd and 4th quartiles, respectively.

Logistic regression models with negative relationship (i.e., beneficial effect [p<0.05]) between drug exposure and the probability of adverse events showed that higher exposure of binimetinib was associated with a decrease in the probability of skin infection, rash events and of arthralgia events. Secondary pharmacology with regard to cardiac safety was assessed by popPK modelling. No relevant change of QTcF from baseline was found, and this supported also results from the pivotal study.

Regarding pharmacodynamic drug interactions the applicant argued that in the pivotal study no potential interacting drugs were used. As currently only few drug substances have the potential to inhibit MEK the potential for such PD interactions is generally low. Potential off-target activity of binimetinib (and encorafenib) to inhibit other kinases is low at the proposed recommended doses.

Regarding genetic differences in PD response of binimetinib UGT1A1 genotype analysis of binimetinib exposure performed in the pivotal study did not establish meaningful changes of predose concentrations between genotypes. Presumably, for a similar concentration safety and efficacy effects could be expected comparable.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetics of binimetinib were studied in healthy subjects and patients with solid tumours and advanced and unresectable or metastatic cutaneous melanoma. After repeat twice-daily dosing concomitantly with encorafenib, steady-state conditions for binimetinib were reached within 15 days with no major accumulation. The mean (CV %) $C_{max,ss}$ was 654 ng/mL (34.7 %) and mean AUC_{ss} was 2.35 ug.h/mL (28.0 %) in combination with encorafenib as estimated by population PK modelling. Binimetinib pharmacokinetics have been shown to be approximately dose-linear.

After oral administration, binimetinib is rapidly absorbed with a median T_{max} of 1.5 hours. Following a single oral dose of 45 mg [^{14}C] binimetinib in healthy subjects, at least 50 % of the binimetinib dose was absorbed. Binimetinib showed low solubility at physiological pH but higher at acidic pH. Administration of a single 45 mg dose of binimetinib with a high-fat, high-calorie meal decreased the maximum binimetinib concentration (C_{max}) by 17 %, while the area under the concentration-time curve (AUC) was unchanged. A drug interaction study in healthy subjects indicated that the extent of binimetinib exposure is not altered in the presence of a gastric pH-altering agent (rabeprazole).

Administration of the commercial formulation of binimetinib with food (HFM) resulted in no significant change in total exposure. Cmax increased with a LFM (29%) but decreased with a HFM (17%). Both a high fat and low-fat meal have only a small effect on Cmax, therefore it can be agreed the drug can be taken without regard for food.
The plasma protein binding has been measured at a range of physiologically relevant concentrations and is 97.2 % bound to human plasma proteins *in vitro*. Binimetinib is more distributed in plasma than blood. In humans, the blood-to-plasma ratio is 0.718. Following a single oral dose of 45 mg [^{14}C] binimetinib in healthy subjects, the apparent volume of distribution (Vz/F) of binimetinib is 374 L.

Following a single oral dose of 45 mg [^{14}C] binimetinib in healthy subjects, the primary biotransformation pathways of binimetinib observed in humans include glucuronidation, N-dealkylation, amide hydrolysis, and loss of ethane-diol from the side chain. 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 catalyse the formation of the active metabolite, which represents less than 20 % of the binimetinib exposure clinically.

Following a single oral dose of 45 mg [^{14}C] binimetinib in healthy subjects, a mean of 62.3 % of the radioactivity was eliminated in the feces while 31.4 % was eliminated in the urine. In urine, 6.5 % of the radioactivity was excreted as binimetinib. The mean (CV %) apparent clearance (CL/F) of binimetinib was 28.2 L/h (17.5 %). The median (range) binimetinib terminal half-life ($T_{1/2}$) was 8.66 h (8.10 to 13.6 h). In faeces binimetinib was the most abundant radioactive component and accounted for an average value of 29.8% of dose. The most abundant metabolites were M4, an ethane-diol cleavage product, and M15.9, a carboxylic acid formed from amide hydrolysis, accounting for 17.2% and 6.7% of the dose, respectively. All other metabolites were present at ≤ 2.7% of the dose. In urine binimetinib was the most abundant radioactive component and accounted for 5.3% to 8.1% of the administered radioactive dose, with an average value of 6.5%. The most abundant metabolites were M10.9 (direct glucuronide of binimetinib), M3 (AR00426032, N-demethylated binimetinib), and M10.2 (another direct glucuronide of binimetinib), accounting for 6.2%, 5.1% and 4.2% of the dose, respectively. All other metabolites were present at ≤ 3.2% of the dose.

Given the 31.7% unchanged in faeces, biliary elimination of binimetinib cannot be discounted. The elimination appears mainly hepatic. The major route of elimination appears to be due to metabolism by UGT1A1 but the quantitative contribution is uncertain. Binimetinib is primarily metabolised through UGT1A1 mediated glucuronidation. In clinical study sub-analysis, however, there was no apparent relationship observed between binimetinib exposure and UGT1A1 mutation status. In addition, simulations to investigate the effect of 400 mg atazanavir (UGT1A1 inhibitor) on the exposure of 45 mg binimetinib predicted similar binimetinib C_{max} in the presence or absence of atazanavir. Therefore, the extent of drug interactions mediated by UGT1A1 is minimal, and unlikely clinically relevant; however, as this has not been evaluated in a formal clinical study, UGT1A1 inducers or inhibitors should be administered with caution (see Section 4.5 and 5.2 of the SmPC). UGT1A1 inducers (such as rifampicin and phenobarbital) and inhibitors (such as indinavir, atazanavir, sorafenib) should be co administered with caution.Binimetinib is not an inhibitor of UGT1A1. While encorafenib is a relatively potent reversible inhibitor of UGT1A1, no differences in binimetinib exposure have been observed clinically when binimetinib is co-administered with encorafenib (see section 5.2).

Cytochrome P450 enzymes appear to account for less than 25% of the elimination. Binimetinib does not inhibit CYPs except for CYP 2B6 which had a Ki of 1.7 µM, however the mechanistic static model was used to rule out an interaction. Binimetinib shows induction of CYP 3A4 in vitro and this was investigated in a clinical study. Induction of mRNA for CYP 1A2 and 2B6 is greater than 2-fold (16.5 and 2.6-fold respectively). *In vitro*, CYP1A2 and CYP2C19 catalyse the formation of the active metabolite, AR00426032 (M3) by oxidative N-desmethylation. Binimetinib is a potential inducer of CYP1A2, and caution should be taken when it is used with sensitive substrates (such as duloxetine or theophylline). Binimetinib is a weak reversible inhibitor of CYP1A2 and CYP2C9. Inducers of CYP1A2 enzymes (such as carbamazepine and rifampicin) and inducers of Pgp transport (such as Saint John's wort or phenytoin) may decrease binimetinib exposure, which could result in a decrease of efficacy.

Binimetinib is a weak inhibitor of OAT3, and caution should be taken when it is used with sensitive substrates (such as pravastatin or ciprofloxacin) and no clinicallly significant drug-drug interactions caused by binimetinib on other transporters is expected.

Binimetinib is not an inhibitor of Pgp, BCRP, OAT1, OCT1, OCT2, MATE-1, MATE-2k or BSEP. It is a weak inhibitor of OATP1B1 and 1B3, but it can be agreed this does not appear to be clinically relevant concentrations. In addition, as 30% is eliminated unchanged in faeces, therefore biliary excretion, possibly by Pgp, cannot be discounted. In vitro experiments indicate that binimetinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Inhibition of P-gp or BCRP is unlikely to result in a clinically important increase in binimetinib concentrations as binimetinib exhibits moderate to high passive permeability. In vitro studies also demonstrated that binimetinib is a P-gp and BCRP substrate, but the effects of inhibitors of these substrates on the PK of binimetinib in vivo has not been investigated.

Binimetinib is metabolised by UGTs and CYP1A2 is a substrate for Pgp.. Specific inducers of these enzymes have not been studied and may result in a loss of efficacy.

There do not appear to be any major metabolites of binimetinib. M3 is stated to be equipotent and attributes less than 20% of binimetinib exposure. The plasma protein binding of metabolite M3 has been determined in all relevant species and is 95.26% in man.

Binimetinib appears essentially linear over the dose range of 20 to 100 mg, however there may be some less than proportional increase at steady state in patients at does above 30 mg but data is limited.

Modest accumulation is seen following multiple dosing, ~1.3 fold in patients following 45 mg. This is consistent with the calculated half-life. The data is based on a comparison of Day 1 to Day 15. Data from the midazolam study shows that steady state is achieved by Day 8 which is slightly longer than may be expected based on the half-life.

The exposure appears to be slightly higher in patients compared to healthy volunteers. In the POPPK analysis clearance is determined to be 32% greater in healthy volunteers.

Exposure to binimetinib 45 mg BID in Study CMEK162X2110 was within the ranges of values observed in the single-agent studies (Studies ARRAY-162-111 and CMEK162X2201), regardless of encorafenib dose level.

Binimetinib undergoes minimal renal elimination. Results from a dedicated clinical study showed that patients with severe renal impairment (eGFR ≤ 29 mL/min/1.73 m^2), had a 29 % increase in exposure (AUC_{inf}), a 21 % increase in C_{max}, and a 22 % decrease in CL/F compared to matching healthy subjects. These differences were within the variability observed for these parameters in both cohorts of this study (25 % - 49 %) and the variability previously observed in patient clinical studies, hence these differences are unlikely to be clinically relevant. It is agreed that based on these PK results no dose adjustment is recommended for patients with renal impairment (see section 5.2).

The effects of renal impairment on the pharmacokinetics of binimetinib in combination with encorafenib have not been evaluated clinically.

As binimetinib is primarily metabolised and eliminated via the liver, patients with moderate to severe hepatic impairment may have increased exposure. Results from a dedicated clinical study with binimetinib only indicate similar exposures in patients with mild impairment (Child-Pugh Class A) and subjects with normal liver function. While an increase in dose-normalised (total) binimetinib exposure was only small with mild impairment, a two-fold increase in total binimetinib exposure (AUC) was observed in patients with moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment (see section 4.2) and clearance reduced to about 50%. In contrast to binimetinib, the plasma concentration of the metabolite AR00426032 decreased with increasing hepatic impairment. This increase expends to three fold in both moderate and severe hepatic impairment when considering unbound binimetinib exposure (see section 4.2).

No dose adjustment is required in patients with mild hepatic impairment (Child Pugh A).

As encorafenib is not recommended in patients with moderate (Child Pugh B) or severe hepatic impairment (Child-Pugh C), administration of binimetinib is not recommended in these patients. (see section 4.2 of encorafenib SmPC).

Binimetinib has not been evaluated in patients with Gilbert's disease. The main route of hepatic transformation of binimetinib being glucoronidation, the decision for treatement should be made by the treating physician taking into account the individual benefit-risk.

Based on a population pharmacokinetic analysis, age or body weight do not have a clinically important effect on the systemic exposure of binimetinib. Based on a population pharmacokinetic (PK) analysis, the PK of binimetinib were similar in males as compared with females. There are insufficient data to evaluate potential differences in the exposure of binimetinib by race or ethnicity.

An analysis performed with the POPPK model does not show a significant effect for a 79-year-old compared to a 59 or 75-year-old. Data has been provided for different age categories based on Bayesian PK parameters. There is evidence of a slight decrease in clearance in older patients however

this does not seem to be large enough to require a dose adjustment. No dose adjustment is required for patients aged 65 years and older (see section 5.2).

It is unknown whether binimetinib or its active metabolite are excreted in human. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue binimetinib therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Exposure – Response Relationship: Binimetinib in Combination with Encorafenib

When analysing ORR, a relationship between binimetinib AUCss and the probability of ORR shows no positive or negative trend. This was observed for part 1 with Combo450 and for part 2 in Combo300. Overall, results derived with Cox proportional hazard models are consistent with those derived for ORR and exposure-response observations from Kaplan-Meier plots, whereby baseline LDH was the strongest prognostic factor of death or progression. The results of these analyses indicated that higher binimetinib exposure was associated with longer PFS than lower exposure (updated analyses Combo 450 Part 1: 16.6 and 12.7 months, respectively), whereas high and low encorafenib exposure showed an inverse relationship with PFS (updated analyses Combo 450 Part 1: 9.36 and 16.5 months, respectively). All groups showed longer PFS than the vemurafenib control arm (7.33 months).

With the responses, the applicant submitted corresponding analyses for OS. These showed a comparable pattern: with higher than median binimetinib AUCss OS of 39.5 months, with lower AUCss 29.6 months; and for encorafenib inversely a longer OS with lower AUCss (36.8. vs. 23.1 months).

For part 2, with Combo300, the new analyses for PFS were comparable for binimetinib: higher than median AUCss 13.4 months, lower AUCss 11.1 months. Here, no effect of encorafenib exposure as in part 1 was observed.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics and pharmacodynamic aspects of binimetinib are generally well presented and considered sufficiently well characterised. The relevant information has been included in section 4.5 and 5.3 of the SmPC.

The CHMP requests the following measures to address the issues related to pharmacology:

- DDI cocktail study: OATP and BCRP will be explored in the ongoing DDI study with rosuvastatin (study ARRAY-818-103)
- Overall survival results stratified by LDH level for Combo 300 and Enco 300 (Part 2).
- To collect PK samples from BRAF melanoma patients with moderate and severe hepatic impairment after repeated dosing of encorafenib in combination with binimetinib to determine the plasma concentrations in relation to administered dose and AEs observed to guide dosing recommendations in these patient populations.

The CHMP recommends the applicant to submit the following measures to address the issues related to pharmacology:

- The applicant should commit to submit the results of the planned biomarker analyses for Study B2301 (from all 3 treatment arms) for evaluation as soon as available, to support the synergistic pharmacodynamic activity of encorafenib in combination with binimetinib. Genomic analysis of baseline samples remaining after centralized BRAF testing. As indicated in the protocol, genomic alterations in BRAF, HRAS, KRAS, NRAS, PTEN, cKIT, PIK3CA, MAP2K1,

MAP2K2, ARAF, c-MET, CRAF, EGFR and CCND1 may be explored to find a potential association between baseline mutations and efficacy outcomes.

- The relationship between baseline mutations and efficacy outcomes should be performed, and a date provided to submit the results.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

The dose recommended for binimetinib and the administration schedule for use in combination with encorafenib in patients with BRAF V600 mutation-positive melanoma is 45 mg BID. This corresponds to 0.35 µg/mL and 2.1 µg.hr/mL in terms of Cmax and AUC0-12h at steady state in humans.

Clinical studies relevant in the determination of binimetinib dose selection are presented in the Table 33 below.

Table 33: Clinical Studies Relevant in Determination of Binimetinib Dose Selection

Study No.	Study Objective, Population	No. of Patients Receiving Binimetinib	Binimetinib Dose	Efficacy Endpoint
ARRY-162-0601	Single ascending dose in healthy subjects	Planned: 20 Actual: 20	5, 10, 20, 30 and 40 mg	None
ARRY-162-0602	Multiple ascending dose in healthy subjects	Planned: 46 Actual: 38	5, 10, 20, 40 and 60 mg QD, 20 mg BID and 80 mg single dose	None
ARRAY-162-111	MTD/RP2D-finding study in patients with advanced solid tumors	Planned: 95 (30 dose escalation, 65 expansion) Actual: 93 (19 dose escalation, 74 expansion)	30, 45, 60, 80 mg BID	Objective response rate
CMEK162X2201	Efficacy/safety in BRAF or NRAS mutation-positive cutaneous melanoma	Planned: 156 (100 NRAS, 56 BRAF) Actual: 183 (117 NRAS, 66 BRAF)	45, 60 mg BID	Objective response rate

Sources: Synopses of Individual Studies, Tabular Listing of All Clinical Studies

Key: BID: twice daily, BRAF: b-raf proto-oncogene serine/threonine-protein kinase, MTD: maximum tolerated dose, No.: number, NRAS: neuroblastoma ras viral oncogene homolog, QD: once daily, RP2D: recommended phase 2 dose.

In study **ARRY-162-0601**, healthy subjects received single, escalating doses of 5, 10, 20, 30 and 40 mg binimetinib or matching placebo. Twenty subjects (4 subjects per dose level) received treatment with binimetinib and 1 subject per dose level received placebo. Headache was the most common adverse in this study. Clinical laboratory results, vital signs, electrocardiograms and physical examinations indicated no safety concern of a single dose of binimetinib ranging from 5 mg to 40 mg.

In study **ARRY-162-0602**, healthy subjects received escalating doses of 5, 10, or 20 mg Once Daily (QD) binimetinib, 20 mg BID binimetinib, 40 or 60 mg QD binimetinib for 14 days, a single dose of 80 mg binimetinib or matching placebo. A total of 50 subjects were enrolled and 44 completed the study. The most commonly reported adverse events were diarrhoea, headache, rash and acne. There was no evidence that diarrhoea or headache was dose-related and none of these events led to discontinuation

of study drug. Adverse events in the Skin and Subcutaneous Tissue Disorders system organ class occurred with the greatest incidence in the 20 mg BID, 40 mg QD, and 60 mg QD binimetinib groups.

The recommended Phase 2 dose (RP2D) of binimetinib monotherapy was determined in **Study ARRAY-162-111**, a Phase 1 dose-escalation study in patients with advanced cancer to determine a maximum tolerated dose (MTD) following 30, 45, 60, and 80 mg BID binimetinib. The primary objectives were to determine the Maximum Tolerated Dose (MTD) and to characterize the safety and PK of binimetinib. Nineteen patients with advanced solid tumours received binimetinib in the Dose-escalation Phase. Four dose levels were evaluated: 30 mg BID, 45 mg BID, 60 mg BID and 80 mg BID. Two of 4 patients receiving 80 mg BID experienced Dose Limiting Toxicities (DLTs), thus the 80 mg BID dose was declared non-tolerable. Seven patients were enrolled at 60 mg BID and no DLTs were observed; therefore, 60 mg BID was declared the MTD. Following completion of the Dose-escalation Phase, 74 patients were enrolled in the Expansion Phase, including 28 patients in the biliary cancer cohort at 60 mg BID dose, 31 patients in *KRAS*-mutant CRC cohort with 6 patients at 60 mg BID and 25 at 45 mg BID dose, and 15 patients in the BRAF-mutant CRC cohort at 45 mg BID dose. The incidence of adverse events resulting in reduction of binimetinib dose were reported at a 3-fold higher incidence in patients in the 60 mg BID dose group compared with the 45 mg BID dose group, and resulted in the decision to discontinue evaluation of the 60 mg BID dose in this study, thus 45 mg BID was determined to be the RP2D.

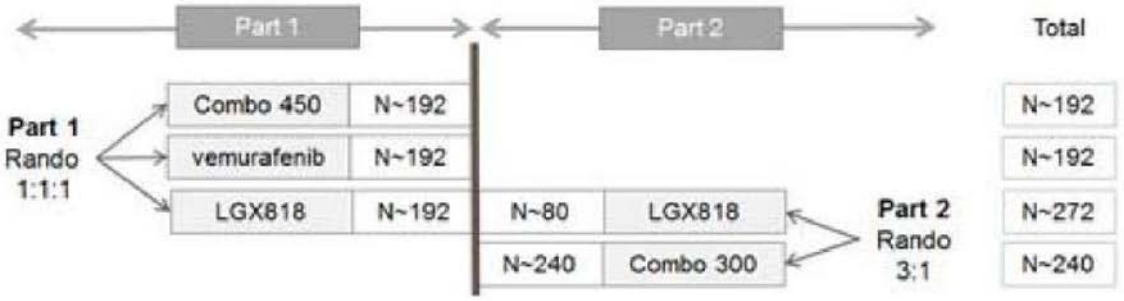
The safety and efficacy of binimetinib monotherapy was assessed in the Phase 2 study, **CMEK162X2201**, conducted in patients with advanced and unresectable or metastatic cutaneous melanoma harbouring a *BRAF* V600E or *NRAS* mutation. Patients received a dose of either 45 or 60 mg BID binimetinib, which demonstrated preliminary signs of antitumour activity. Twenty-five patients initially received 60 mg BID binimetinib but subsequently had their dose reduced to 45 mg BID due to the occurrence of 2 serious AEs with suspected relationship to the study drug. The results confirmed 45 mg BID to be a generally well-tolerated dose with an acceptable safety profile in patients with *BRAF* V600E mutation-positive advanced cutaneous melanoma.

2.5.2. Main study(ies)

COLUMBUS: 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

Methods

Figure 1: Study CMEK162B2301 Randomisation Scheme



BID: twice daily; Combo 300: encorafenib 300 mg QD in combination with binimetinib 45 mg BID; Combo 450: binimetinib 45 mg BID in combination with encorafenib 450 mg QD; LGX818: encorafenib 300 mg monotherapy; QD: once daily; Rando: randomised.

PART 1

Study Participants

Inclusion Criteria

1. Signed written informed consent;
2. Male or female patient, age ≥ 18 years;
3. Histologically confirmed diagnosis of locally advanced, unresectable or metastatic cutaneous melanoma or unknown primary melanoma AJCC Stage IIIB, IIIC or IV;
4. Presence of BRAF V600E and/or V600K mutation in tumor tissue prior to enrollment, as determined by a Sponsor designated central laboratory(ies);
5. Naive untreated patients or patients who have progressed on or after prior first-line immunotherapy for unresectable locally advanced or metastatic melanoma;

Note: Prior adjuvant therapy is permitted (e.g. IFN, IL-2 therapy, any other immunotherapy, radiotherapy or chemotherapy), except the administration of BRAF or MEK inhibitors.

6. Evidence of at least one measurable lesion as detected by radiological or photographic methods according to guidelines based on RECIST version 1.1 (Appendix 2);

Note: A previously irradiated lesion is eligible to be considered as a measurable lesion provided that there is objective evidence of progression of the lesion since discontinuation of therapy and prior to starting study drug.

7. ECOG performance status of 0 or 1;
8. Adequate bone marrow, organ function and laboratory parameters:

- Absolute neutrophil count (ANC) $\geq$ 1.5 x 10^9/L,
- Hemoglobin (Hgb) $\geq$ 9 g/dL without transfusions,
- Platelets (PLT) $\geq$ 100 x 109/L without transfusions,
- AST and/or ALT $\leq$ 2.5 × upper limit of normal (ULN); patient with liver metastases $\leq$ 5 ×ULN,
- Total bilirubin $\leq$ 2 × ULN,
- Creatinine $\leq$ 1.5 mg/dL, or calculated creatinine clearance (determined as per Cockcroft-Gault) $\geq$ 50mL/min;

9. Adequate cardiac function:
    - left ventricular ejection fraction (LVEF) $\geq$ 50% as determined by a multigated acquisition (MUGA) scan or echocardiogram,
    - triplicate average baseline QTc interval $\leq$ 480 ms;
10. Able to take oral medications;
11. Patient is deemed by the Investigator to have the initiative and means to be compliant with the protocol (treatment and follow-up);
12. Negative serum β-HCG test (female patient of childbearing potential only) performed within 72 hours prior to first dose.

Exclusion criteria

1. Any untreated central nervous system (CNS) lesion. However, patients are eligible if: a) all known CNS lesions have been treated with radiotherapy or surgery and b) patient remained without evidence of CNS disease progression $\geq$ 4 weeks and c) patients must be off corticosteroid therapy for $\geq$ 3 weeks.
2. Uveal and mucosal melanoma;
3. History of leptomeningeal metastases;
4. History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes);
5. History of allogeneic bone marrow transplantation or organ transplantation;
6. History of Gilbert’ s syndrome;
7. Previous or concurrent malignancy with the following exceptions:
    - adequately treated basal cell or squamous cell carcinoma of the skin (adequate wound healing is required prior to study entry),
    - in situ carcinoma of the cervix, treated curatively and without evidence of recurrence for at least 3 years prior to the study,
    - or other solid tumor treated curatively, and without evidence of recurrence for at least 3 years prior to study entry; (note: based on mechanism of action, BRAF inhibitors may cause progression of cancers associated with RAS mutations. Thus, benefits and risks should be

carefully considered before administering a BRAF inhibitor to patients with a prior cancer associated with RAS mutation).

8. Prior therapy with a BRAF inhibitor (including but not limited to vemurafenib, dabrafenib, LGX818, and XL281/BMS-908662) and/or a MEK inhibitor (including but not limited to trametinib, AZD6244, MEK162, GDC-0973 and RDEA119);
9. Any previous systemic chemotherapy treatment, extensive radiotherapy or investigational agent other than immunotherapy, or patients who have received more than one line of immunotherapy for locally advanced unresectable or metastatic melanoma; Note: Ipilimumab or other immunotherapy treatment must have ended at least 6 weeks prior to randomization. Chemotherapy given as part of isolated limb perfusion, regional or intralesional treatment will not be considered systemic treatment.
10. Impaired cardiovascular function or clinically significant cardiovascular diseases, including any of the following:
    - History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) <6 months prior to screening,
    - Symptomatic chronic heart failure, history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality <6 months prior to screening except atrial fibrillation and paroxysmal supraventricular tachycardia;
11. Uncontrolled arterial hypertension despite medical treatment;
12. Known positive serology for HIV(Human immunodeficiency virus), active hepatitis B, and/or active hepatitis C infection;
13. Patients who have neuromuscular disorders that are associated with elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy);
14. Patients who are planning on embarking on a new strenuous exercise regimen after first dose of study treatment.
15. Impairment of gastrointestinal function (e.g., active ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome);
16. Any other condition that would, in the Investigator’ s judgment, contraindicate the patient’ s participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g., infection/inflammation, intestinal obstruction, unable to swallow medication, social/ psychological issues, etc.;
17. Patients who have undergone major surgery or radiotherapy $\leq$ 3 weeks prior to starting study drug or who have not recovered from side effects of such procedure;
18. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test;
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception throughout the study and for 8 weeks (6 months for women of child-bearing potential randomized to vemurafenib) after study drug discontinuation.

20. Medical, psychiatric, cognitive or other conditions that may compromise the patient's ability to understand the patient information, give informed consent, comply with the study protocol or complete the study.

21. Patients taking non-topical medication known to be a strong inhibitor of CYP3A4.

Treatments

Encorafenib was supplied as 50mg and 100mg capsules (the MAA is for 50mg and 75mg capsules). Patients were not to have eaten anything for 2 hours before and 1 hour after the morning dose of study drug.

Patients received study treatment until progressive disease (PD) per RECIST v1.1 as determined by the blinded independent review committee (BIRC), unacceptable toxicity, withdrawal of consent, death, physician decision or early termination of the study.

The permitted dose reduction levels for encorafenib were 300 mg, 200 mg, 100 mg and 50 mg QD with specific recommendations regarding eye disorders, CK elevation, decreased LVEF, QTc prolongation, skin, gastrointestinal and liver-related AEs. Dose re-escalation was permitted if toxicity improved to ≤ Grade 1, except for QT prolongation (QTcF >500msec). A patient in the Combo 450 arm who permanently discontinued binimetinib could continue encorafenib monotherapy but, if encorafenib was permanently discontinued, then binimetinib had to be discontinued due to its limited efficacy in monotherapy. Patients requiring treatment interruption >28 days were to be permanently discontinued.

Objectives

The primary objective was to determine whether treatment with Combo 450 prolongs progression-free survival (PFS) compared with vemurafenib in patients with *BRAF* V600 mutant locally advanced unresectable or metastatic melanoma. This was addressed by Part 1 of the study.

The key secondary objectives were to determine the contribution of binimetinib to the combination by comparing the PFS of Combo 450 vs. encorafenib (Part 1) and to further quantify the contribution of binimetinib to the combination by comparing the PFS of Combo 300 vs. encorafenib (Part 2).

Other secondary objectives included:

Part 1 only – to compare the treatment effect of Combo 450 vs. vemurafenib in terms of overall survival (OS); to estimate the treatment effect of combo 450 vs. encorafenib in terms of OS; to determine the safety and tolerability of Combo 450 and encorafenib in this patient population

Part 2 only- to estimate the safety and tolerability of combo 300 vs. encorafenib in this patient population; to estimate the safety and tolerability of Combo 300 vs. Combo 450 in this patient population; to estimate the treatment effect of Combo 300 vs. encorafenib in terms of OS; to estimate the treatment effect of Combo 300 vs. vemurafenib in terms of PFS and OS; to estimate the treatment effect of Combo 300 vs. Combo 450 in terms of PFS and OS.

Parts 1 & 2- to estimate the treatment effect of encorafenib vs. vemurafenib in terms of PFS and OS; to assess objective response rate (ORR) by treatment arms; to describe time to response (TTR); to assess disease control rate (DCR); to evaluate duration of response (DOR); to compare the patient-reported outcomes (PROs) and the ECOG PS between the treatment arms and to characterise the PK of encorafenib and binimetinib in this patient population.

Exploratory objectives included:

Part 1- to assess whether the *BRAF* mutation status in circulating tumour DNA correlates with the *BRAF* mutation status in tumour tissue

Parts 1 & 2- to explore baseline molecular status of genes relevant to RAF/MEK/ERK and PI3K/AKT signalling in tumour tissue and their potential correlation to efficacy outcomes and to explore potential markers of acquired resistance to encorafenib and encorafenib plus binimetinib

Outcomes/endpoints

The **primary efficacy endpoint** of the study was PFS, defined as the time from the date of randomisation to the date of the first documented progression based on tumour assessment read centrally by a BICR according to RECIST v1.1 criteria, or death due to any cause, whichever occurred first. If a patient did not have an event at the time of the analysis cut-off or at the start of any new antineoplastic therapy, PFS was censored at the date of the last adequate tumour assessment. If a patient discontinued treatment for "disease progression", without documented evidence of progression based on RECIST v1.1, it was not to be considered as a PFS event.

The **key secondary** for Part 1 was PFS per BIRC on Combo 450 vs. Enco 300.

Other secondary endpoints

Other secondary efficacy endpoints included:

- OS (time from the date of randomization to date of death due to any cause);
- ORR (proportion of patients with a best overall response of CR or PR, calculated for confirmed and unconfirmed responses separately);
- TTR (time from date of randomization until first documented CR or PR);
- DCR (proportion of patients with a best overall response of CR, PR or stable disease);
- DOR (time from the date of first documented CR or PR to the first documented progression or death due to underlying cancer) and
- the PROs i.e. Functional Assessment of Cancer Therapy Melanoma [FACT-M] v 4, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 [EORTC QLQ-C30] v 3.0 and EuroQoL-5D-5 Level (EQ-5D-5L] v 4.0. The main PRO endpoints were time to definitive 10% deterioration in the FACT-M melanoma subscale and global health status score of the EORTC QLQ-C30; change from baseline in the FACT-M melanoma subscale, EQ-5D-5L, and global health status score of the EORTC QLQ-C30; change from baseline in the other EORTC QLQ-C30 subscales.

Efficacy and PROs were assessed every 8 weeks until week 105 and every 12 weeks thereafter until progression or end of treatment. Patients were then followed every 12 weeks for survival and use of subsequent anticancer therapy. Safety was assessed every 4 weeks. Patients in the combination arms had an ophthalmic exam at the start of each treatment cycle and pre- and post-dose PK samples.

Sample size

For the vemurafenib arm, a median PFS of 7 months was assumed based on results from studies in previously untreated patients and patients who progressed after at least one prior systemic treatment were studied, respectively, where the median PFS values were 6.9 and 6.8 months, respectively.

Based on the dose-escalation results and the dose-expansion results of the Clinical Study CLGX818X2101, the observed median for patients treated with encorafenib was 7.1 months (95% CI 3.7, 14.7) and 7.4 months (95% CI 7.4, not estimable [NE]), respectively. In this less advanced patient population, the median PFS was therefore expected to be around 8 months.

Based on results from Clinical Study CMEK162X2110, Combo 450 was expected to result in a 42% reduction in hazard rate compared to vemurafenib (corresponding to an increase in median from 7 months to 12 months).

The observed benefit with Combo 300 was expected to be lower than with Combo 450. The median PFS was therefore anticipated to be around 11 months.

In study Part 1, patients were randomized in a 1:1:1 ratio to receive Combo 450, encorafenib or vemurafenib. The sample size driver for study Part 1 was the Combo 450 vs. encorafenib comparison. For the comparison of Combo 450 vs. encorafenib, 191 PFS events were required to detect a HR of 0.667 with an 80% power using a log-rank test at a one-sided 2.5% level of significance. For the Part 1 primary comparison, Combo 450 vs. vemurafenib, 145 PFS events were required to detect a HR of 0.58 with a 90% power using a log-rank test at a one-sided 2.5% level of significance.

A total of 576 patients (192 patients in each arm) were planned to be recruited in Part 1 over around 15 months, accounting for 15% loss to follow-up. The primary analysis was to be performed when a sufficient number of PFS events for both the primary and key secondary comparisons were available, which was expected to occur around 22 months after first treatment of the first patient.

In Part 2, the new Combo 300 arm was added. The data already collected in Part 1 for the encorafenib arm represented a considerable amount of information; therefore, the randomization ratio for Combo 300 to encorafenib in Part 2 was 3:1.

Considering a 3:1 randomization ratio in the second part of the study and aiming for a similar number of patients in the Combo 300 and the encorafenib arm (combining Part 1 and 2), 320 additional patients were to be randomized (80 in the encorafenib arm and 240 in the Combo 300 arm).

The Part 2 PFS Analysis was to be performed when approximately 340 PFS events had occurred in total in the encorafenib (both parts) and Combo 300 arms. Based on the differential follow-up and expected median PFS times, it was expected that approximately 330 of these events would contribute to the HR estimate and log-rank test, and would result in approximately 80% power to detect a HR of 0.727 (8/11) at a one-sided 2.5% level of significance. This was anticipated to occur approximatively 37 months after first treatment of the first patient.

Randomisation

In Part 1, approximately 576 patients were to be randomised in a 1:1:1 ratio to one of the 3 treatment arms.

Randomisation was stratified by AJCC stage (IIIB + IIIC + IVM1a + IVM1b vs. IVM1c); ECOG PS (0 vs. 1), BRAF mutation status (V600E vs. V600K) and prior first-line immunotherapy for unresectable or metastatic disease (yes vs. no).

Prior first line immunotherapy (yes vs. no) added with Protocol Amendment 2 (post enrolment of 2 patients), when inclusion of this patient group was allowed.

BRAF mutation status (V600E vs. V600K) was removed as a stratification factor with Protocol Amendment 2, as the V600K stratum was expected to be very small.

Blinding (masking)

The study was open label. However, blinded tumour assessment data read centrally by a BIRC were used in the primary efficacy analysis.

Statistical methods

The following analysis populations were defined:

The Full Analysis Set (FAS) was defined according to the Intention-to-Treat (ITT) principle, and consisted of all randomized patients. Following the ITT principle, patients were analyzed according to the treatment and stratification factors they were assigned to at randomization.

The Per-protocol Set (PPS) consisted of all patients from the FAS without any major protocol deviations and who received at least one dose of study medication.

The Safety Set included all patients who received at least one dose of the study medication and had at least one valid post-baseline safety evaluation. Patients were analyzed according to the study treatment they actually received.

The Pharmacokinetic Analysis Set (PAS) consisted of all patients who received at least one dose of encorafenib or binimetinib and had at least one evaluable post-baseline encorafenib or binimetinib concentration measurement. The same definition applied to the Japanese subgroup.

All efficacy analyses were performed using the FAS, unless otherwise specified.

The primary and key secondary efficacy comparisons were based on PFS, 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. Censoring rules to be applied to the PFS endpoint are described in the following table.

Table 34: Censoring rules to be applied to the progression-free survival analysis

	Situation	Event Date	Outcome
A[a]	No baseline assessment	Date of randomization	Censored
B	Progression or death at or before next scheduled assessment	Date of progression (or death)	Progressed
C1	Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
C2	Progression or death after two or more missing assessments	Date of last adequate tumor assessment*	Censored
D	No progression	Date of last adequate tumor assessment*	Censored
E	Treatment discontinuation due to "Disease progression" without documented progression, i.e., clinical progression based on investigator claim	N/A (not considered as an event, patient without documented PD should be followed for progression after discontinuation of treatment)	Information ignored
F	New anticancer therapy given	Date of last adequate tumor assessment*	Censored

Abbreviations: PD = progressive disease
[a] The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case a PFS event at the date of death is counted
* tumor assessment with non-missing and non-unknown overall lesion response

Blinded tumor assessment data read centrally by a BIRC were used in the primary efficacy analysis. The local Investigator's assessments were used in a supportive analysis of PFS.

The primary analysis was the comparison of the distribution of PFS between Combo 450 and vemurafenib using a stratified log-rank test at a one-sided 2.5% cumulative level of significance.

The null and the alternative hypothesis were defined as follows:

$H_0: S_{C450}(t) \leq S_{vem}(t)$ vs $H_A: S_{C450}(t) > S_{vem}(t), t \geq 0$ where $S_{vem}(t)$ is the survival distribution function of PFS in the control arm (i.e. vemurafenib) and $S_{C450}(t)$ is the survival distribution function of PFS in the experimental arm (i.e. Combo 450).

Progression-free survival was analyzed based on the data from the FAS according to the treatment arm and 2 of the stratification factors (cancer stage and ECOG PS) patients were randomized to. Due to the relatively low expected prevalence of patients with prior immunotherapy (around 15%), the 2 prior immunotherapy strata (yes and no) were combined at the time of the analysis to avoid small or empty strata. The same principle applied to all stratified tests and models in this study.

The distribution of PFS was described in tabular and graphical format by treatment arm using Kaplan-Meier methods, reporting estimated median (in months) with 95% confidence interval (CI), 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points (including at least 2, 4, 6, 8, 10, 12 and 14 months).

A Cox regression model stratified by randomization stratification factors was used to estimate the HR of PFS, along with 95% CI based on the Wald test.

To control type I error, a hierarchical testing procedure was used and the secondary endpoint of OS Combo 450 vs vemurafenib was to be tested only if the primary and key secondary PFS comparisons were statistically significant.

Data cut-off for Part 1 was to take place once the planned number of patients had been randomised to Part 1 (i.e. 576 patients) and sufficient PFS events were available for the final primary and Part 1 key secondary comparison (i.e.145 PFS events for Combo 450 vs. vemurafenib and 191 PFS events for

Combo 450 vs. encorafenib). The analysis was performed at 204 PFS events for Combo 450 vs. vemurafenib and 223 PFS events for Combo 450 vs. Enco 300.

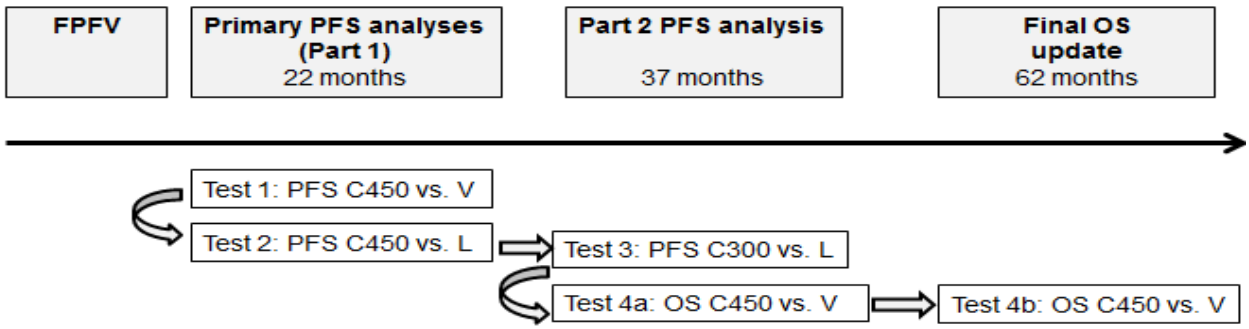


Figure 7: Timing of Testing of Primary and Key Secondary Endpoints (hierarchical testing sequence)

C450= Combo 450; C300= Combo 300; L=LGX818 (encorafenib); V= vemurafenib

Overall survival was defined as the time from the date of randomization to the date of death due to any cause. If a death was not observed by the date of analysis cutoff, OS was to be censored at the date of last contact. Survival time for patients with no post-baseline survival information was to be censored on the date of randomization. For analysis of OS, a group sequential design with one interim analysis (at time of PFS analysis (Part 2)) was planned to be used. To maintain the overall type-I error rate for the trial, the type-1 error rate was based on a α-spending function using a Gamma function with parameter 1. At the time of the Primary PFS Analysis (Part 1), no formal testing of OS was performed in order to preserve Sponsor blinding to OS and maintain the integrity of the planned first interim analysis.

Secondary efficacy variables were analyzed in the FAS and were to include ORR, TTR, DCR, DOR and PROs.

The BIRC assessments were used for the main analyses of best overall response (BOR), ORR, TTR, DCR and DOR. ORR and DCR were presented by treatment arm along with exact 95% CI using the Clopper-Pearson method.

Time to response and duration of response were descriptively analyzed using the Kaplan-Meier method.

The change in tumor size was to be depicted using waterfall plots presenting the best percentage change from baseline in the sum of the diameter of all target lesions. These plots were to display the best percentage change from baseline in the sum of the diameter of all target lesions for each patient.

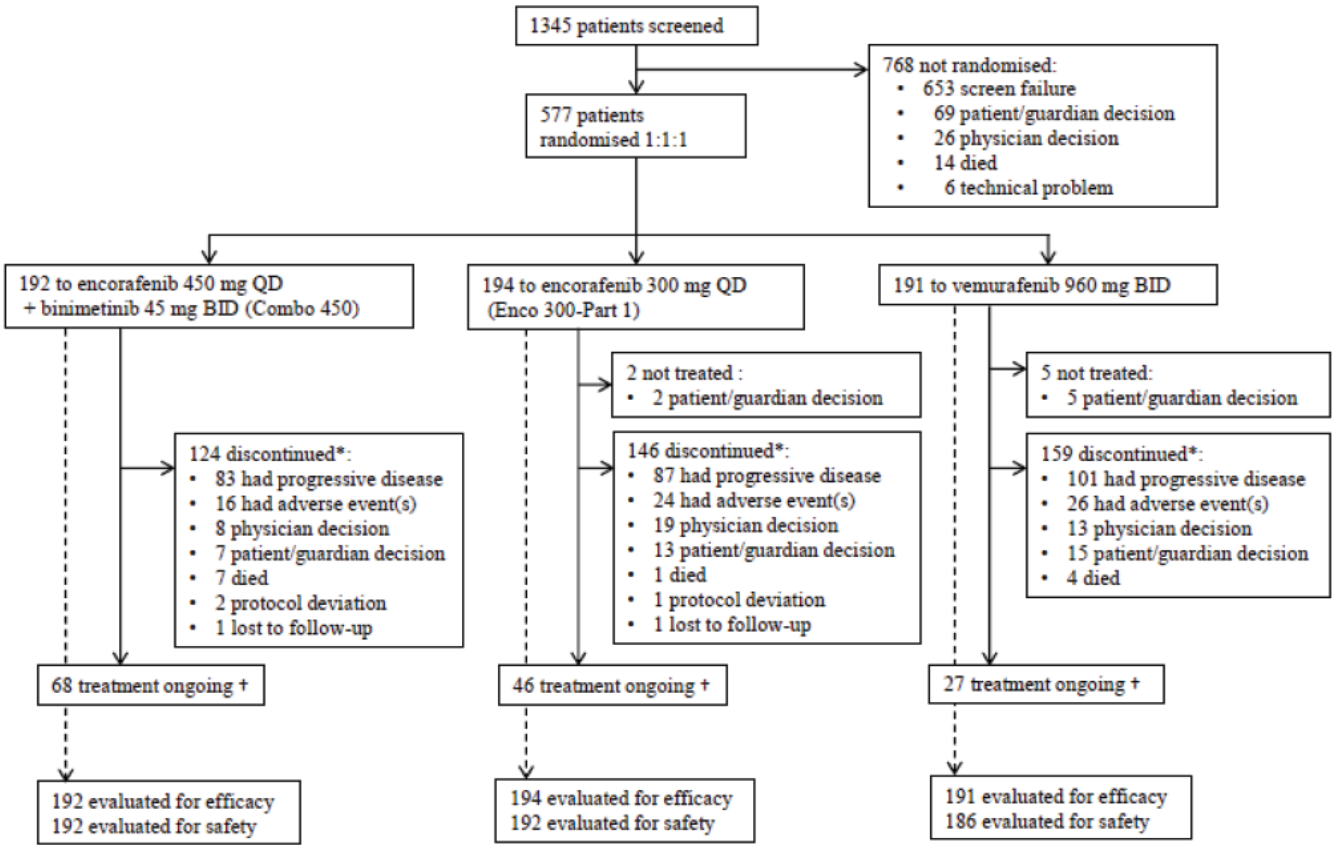
Health-related QoL data were collected via PROs. The FACT-M, EQ-5D-5L and EORTC QLQ-C30 patient questionnaires were used in this study. Health-related QoL data were analyzed using the FAS. The FACT-M melanoma subscale, index score of EQ-5D-5L and the global health status/QoL score of the EORTC QLQ-C30 were identified as the primary PRO variables of interest. Physical functioning, emotional functioning and social functioning scale scores of the EORTC QLQ-C30 were considered as secondary.

The primary PRO analysis was to assess the difference in distribution of the time to definitive 10% deterioration in the FACT-M subscale among the treatment arms in the full analysis set (FAS). Only assessments collected while the patient was on treatment and at the EOT visit were included.

Results

Participant flow

Patient Flow Chart for Part 1 of Study CMEK162B2301



BID: Twice daily; QD: once daily; * Primary reason; † at the time of date cutoff of 19 May 2016

Recruitment

Patients were randomised at 162 sites in 28 countries; 20 sites in North America, 124 sites in Europe and 18 sites in selected countries from the rest of the world. A small number were enrolled per site so data from all sites were pooled.

Conduct of the study

The proportion of patients with at least one protocol deviation was similar among the 3 treatment arms (62.0% Combo 450, 66.0% encorafenib, 64.4% vemurafenib arm). Most protocol deviations were due to key procedures not performed as per protocol (48.4% Combo 450, 52.6% encorafenib, 54.5% vemurafenib arm). Deviations due to eligibility criteria not met were reported in each treatment arm (8.9% Combo 450 arm, 10.8% encorafenib arm, 4.7% vemurafenib arm).

There were 4 amendments to the original study protocol (dated 13 May 2013).

Version 1, Amendment 1 (3 October 2013) was issued before any patients were randomised and included clarification that patients known to be NRAS mutation positive should not be selected for pre-screening.

Version 2, Amendment 2 (20 December 2013) after 2 patients had been randomised allowed inclusion of patients progressing on or after first line immunotherapy.

Version 3, Amendment 3 (4 November 2014) was issued when 364 patients had been randomised. Part 2 was added. Consequently, allocation to Part 1 was reduced, the primary objective of analysis of PFS of encorafenib monotherapy vs. vemurafenib was changed to a secondary endpoint and the key secondary endpoint of overall survival for Combo 450 vs. vemurafenib was changed to a secondary endpoint to be tested hierarchically after the Part 2 key secondary endpoint.

Version 4, Amendment 4 (13 Jul 2015), documented a change in study sponsorship.

At the time of the primary PFS analysis (data cut-off 19 May 2016), the required number of survival events had not occurred for analysis of overall survival (OS). On 14 October 2016, the DMC reviewed un-blinded data from Part 1 (data cut-off 19 May 2016) and un-blinded survival data, to which the Sponsor (Array) and Pierre Fabre remained blinded. The DMC recommended the following:

- Terminate the planned analyses and inform all patients (in Parts 1 and 2) of the Part 1 results.
- Inform patients in the vemurafenib arm that a combination of commercially available BRAF and MEK inhibitors may be a better alternative regimen.

There were no specific recommendations regarding the encorafenib monotherapy arm. The decision to continue encorafenib monotherapy or change to a BRAF/MEK inhibitor combination was to be based on a discussion between the patient and physician.

To minimise the delay in the timing of the OS interim analysis, the applicant proposed that the protocol be amended to de-couple the Part 1 OS analysis from the primary Part 2 PFS analysis. The timing of the Part 1 OS analysis became event driven; the interim OS data was submitted with the response to the D120 list of questions.

Per Protocol Amendment 5.0, two OS analyses of Combo 450 vs. vemurafenib were planned based on the number of OS events in the Combo 450 and vemurafenib arms combined:

Part 1 OS Interim Analysis: The primary OS analysis was to be performed when approximately 232 OS events were observed

Final OS Update: to be performed when approximately 309 OS events were observed

The data cut-off date for this Part 1 OS interim analysis was 7 November 2017, by which time a total of 232 OS events were observed in the Combo 450 and vemurafenib arms combined in Part 1 of the study.

Table 35: Reasons Leading to Exclusion of Patients from Per-protocol Set (Full Analysis Set, Part 1)

Reason	Combo 450 N=192 n (%)	Encorafenib N=194 n (%)	Vemurafenib N=191 n (%)
Patients excluded from Per-protocol set	4 (2.1)	10 (5.2)	7 (3.7)
Patient did not receive at least one dose of study medication	0	2 (1.0)	5 (2.6)
No histologically confirmed diagnosis of unresectable or metastatic cutaneous melanoma or unknown primary melanoma (stage IIIB, IIIC to IV per AJCC) [a]	1 (0.5)	1 (0.5)	0
Not positive for *BRAF* V600 mutation [a]	0	2 (1.0)	0
Prior treatment for unresectable or metastatic cutaneous melanoma other than immunotherapy [a]	1 (0.5)	0	0
Prior treatment with a RAF and/or MEK inhibitor [a]	0	1 (0.5)	0
No measurable lesion as detected by local review of radiological or photographic methods based on RECIST version 1.1 [a]	1 (0.5)	0	1 (0.5)
New anti-neoplastic therapy administered after start of study treatment and prior to first tumor assessment	1 (0.5)	4 (2.1)	1 (0.5)

Baseline data

Table 36: Demographics (Full Analysis Set, Part 1)

Demographic Variable	Combo 450 N=192	Encorafenib N=194	Vemurafenib N=191

Age (years)			
Mean (SD)	56.2 (13.62)	54.6 (12.63)	55.2 (14.18)
Median	57.0	54.0	56.0
Min - Max	20 - 89	23 - 88	21 - 82
Age category (years), n (%)			
< 65	132 (68.8)	154 (79.4)	140 (73.3)
≥ 65	60 (31.3)	40 (20.6)	51 (26.7)
Sex, n (%)			
Female	77 (40.1)	86 (44.3)	80 (41.9)
Male	115 (59.9)	108 (55.7)	111 (58.1)
Race, n (%)			
Caucasian	181 (94.3)	174 (89.7)	166 (86.9)
Asian	5 (2.6)	6 (3.1)	8 (4.2)
Native American	0	2 (1.0)	2 (1.0)
Other	3 (1.6)	2 (1.0)	2 (1.0)
Unknown [b]	2 (1.0)	9 (4.6)	12 (6.3)
Missing [c]	1 (0.5)	1 (0.5)	1 (0.5)
ECOG performance status, n (%) [a]			
0	136 (70.8)	140 (72.2)	140 (73.3)
1	56 (29.2)	54 (27.8)	51 (26.7)

[a] Last non-missing ECOG performance status prior to/at the start of study treatment for patients who took at least one study treatment or prior to/ on Cycle 1 Day 1 for patients who didn't take any study treatment.
[b] Unknown denotes “unknown” was selected on the eCRF.
[c] Missing denotes the race field on the eCRF was not completed.

Table 37: Patient and Disease Characteristics (Full Analysis Set, Part 1)

Disease history	Combo 450 N=192	Encorafenib N=194	Vemurafenib N=191
Primary site of cancer, n (%)			
Skin Melanoma	191 (99.5)	192 (99.0)	190 (99.5)
Unknown	1 (0.5)	2 (1.0)	1 (0.5)
Stage at time of study entry, n (%)			
Stage IIIB	0	2 (1.0)	1 (0.5)
Stage IIIC	9 (4.7)	4 (2.1)	10 (5.2)
Stage IV M1A	26 (13.5)	29 (14.9)	24 (12.6)
Stage IV M1B	34 (17.7)	39 (20.1)	31 (16.2)
Stage IV M1C with elevated LDH	50 (26.0)	50 (25.8)	36 (18.8)
Stage IV M1C with normal LDH	73 (38.0)	70 (36.1)	89 (46.6)
Time from initial diagnosis to onset of metastatic disease (months)			
n	187	191	187
Mean (SD)	37.02 (61.090)	36.45 (62.708)	38.14 (52.994)
Median	15.05	13.04	14.92
Min - Max	0.0 – 448.5	0.0 - 388.8	0.0 - 280.5
Number of organs involved at Baseline [a], n (%)			
1	47 (24.5)	56 (28.9)	45 (23.6)
2	58 (30.2)	52 (26.8)	59 (30.9)
3	45 (23.4)	42 (21.6)	42 (22.0)
>3	42 (21.9)	44 (22.7)	45 (23.6)
LDH at Baseline (U/L)			
n	192	194	191
Mean (SD)	298.7 (368.93)	265.2 (251.21)	239.8 (189.27)
Median	173.0	188.5	174.0
Min - Max	76 - 3590	75 - 1886	57 - 1285
LDH at Baseline [b], n (%)			
Low	0	0	0
Normal	137 (71.4)	147 (75.8)	139 (72.8)
High	55 (28.6)	47 (24.2)	52 (27.2)
Missing	0	0	0

Note: The time from initial diagnosis to onset of metastatic disease are calculated only for patients with metastatic disease. A patient may have multiple metastatic sites. Metastatic sites and organs involved were derived from Diagnosis and Extent of Cancer eCRF page.

[a] For patients with stage IIIB and IIIC at study entry, the number of organs involved at baseline is equal to one and presented as skin.

[b] Low and high categories defined by normal ranges.

Table 38: Prior Antineoplastic Therapy – Overall (Full Analysis Set, Part 1)

	Combo 450 N=192 n (%)	Encorafenib N=194 n (%)	Vemurafenib N=191 n (%)
Any therapy [a]	158 (82.3)	161 (83.0)	165 (86.4)
Medication	62 (32.3)	63 (32.5)	59 (30.9)
Surgery	146 (76.0)	149 (76.8)	157 (82.2)
Radiotherapy	30 (15.6)	42 (21.6)	25 (13.1)
Medication: setting at last treatment			
Adjuvant	52 (27.1)	46 (23.7)	46 (24.1)
Neoadjuvant	0	1 (0.5)	1 (0.5)
Therapeutic - Metastatic	10 (5.2)	16 (8.2)	12 (6.3)
Radiotherapy: setting at last radiotherapy			
Adjuvant	17 (8.9)	20 (10.3)	11 (5.8)
Neoadjuvant	0	1 (0.5)	0
Therapeutic - metastatic	6 (3.1)	11 (5.7)	6 (3.1)
Therapeutic	3 (1.6)	6 (3.1)	4 (2.1)
Palliative	2 (1.0)	4 (2.1)	2 (1.0)
Other	2 (1.0)	0	0
Missing	0	0	2 (1.0)

[a] A patient may have had multiple therapy types.

Table 39: Prior Antineoplastic Therapies – Ipilimumab, anti-PD1/PDL1 or Interferons/Interleukins (Full Analysis Set, Part 1)

	Combo 450 N=192 n (%)	Encorafenib N=194 n (%)	Vemurafenib N=191 n (%)
Any immunotherapy	57 (29.7)	58 (29.9)	57 (29.8)
Ipilimumab	7 (3.6)	10 (5.2)	7 (3.7)
Anti-PD1/PDL1	1 (0.5)	2 (1.0)	0
Interferons/Interleukins	51 (26.6)	51 (26.3)	52 (27.2)
Ipilimumab – Setting [a,b]	n=7	n=10	n=7
Adjuvant	2 (28.6)	1 (10.0)	2 (28.6)
Therapeutic-metastatic	5 (71.4)	9 (90.0)	5 (71.4)
Anti-PD1/PDL1 - Setting [a,b]	n=1	n=2	n=0
Therapeutic-metastatic	1 (100)	2 (100)	0
Interferons/Interleukins – Setting [a]	n=51	n=51	n=52
Adjuvant	47 (92.2)	46 (90.2)	46 (88.5)
Neoadjuvant	0	1 (2.0)	1 (1.9)
Therapeutic-metastatic	4 (7.8)	4 (7.8)	5 (9.6)

PD1 = programmed death 1 (receptor); PDL1 = programmed death (receptor) ligand 1
[a] A patient may have multiple settings.
[b] A patient may have received ipilimumab or anti-PD1/PDL1 in combination.

A similar percentage of patients (29.7% Combo 450, 29.9% Enco 300, 29.8% vemurafenib arm) received prior immunotherapy (metastatic and adjuvant). This was mainly cytokines (interferon/ interleukin); the proportion who received prior ipilimumab was <5% and anti PD1/ anti PDL1 <1%.

The median age of patients was 56 years (range 20¬-89), 58% were male, 90% were Caucasian, and 72% of patients had baseline ECOG performance status of 0. Most patients had metastatic disease (95%) and were Stage IVM1c (64%); 27% of patients had elevated baseline serum lactate dehydrogenase (LDH), and 45% of patients had at least 3 organs with tumour involvement at baseline

and 3.5% had brain metastases. 27 patients (5%) had received prior checkpoint inhibitors (anti-PD1/PDL1 or ipilimumab) (8 patients in Combo 450 arm (4%); 7 patients in vemurafenib arm (4%); 12 patients in Enco 300 arm (6%) including 22 patients in the metastatic setting (6 patients in Combo 450 arm; 5 patients in vemurafenib arm; 11 patients in Enco 300 arm) and 5 patients in the adjuvant setting (2 patients in Combo 450 arm; 2 patients in vemurafenib arm; 1 patient in Enco 300 arm).

Table 40: Anti-neoplastic Therapy Since Study Drug Discontinuation

Discontinued treatment/ not treated	Combo 450 N=124	Encorafenib N=148	Vemurafenib N=164
Subsequent antineoplastic therapy, n (n%)	65 (52.4%)	90 (60.8%)	106 (64.6%)
Subsequent monoclonal antibodies, n (n%)	48 (38.7%)	53 (35.8%)	63 (38.4%)
Subsequent BRAF/ BRAF + MEK inhibitor, n (n%)	17 (13.7%)	35 (23.6%)	55 (33.5%)
Subsequent encorafenib + binimetinib, n (%)	0	4 (2.7%)	5 (3.0%)

A similar proportion of patients in each treatment arm received subsequent treatment with checkpoint inhibitors, mainly pembrolizumab, nivolumab and ipilimumab (34.4% Combo 450 arm, 36.1% encorafenib arm, 39.8% vemurafenib arm).

Numbers analysed

Table 41: Analysis Sets (Part 1)

Analysis Set	Combo 450 N=192 n (%)	Encorafenib N=194 n (%)	Vemurafenib N=191 n (%)	Total N=577 n (%)
Full Analysis Set [a]	192 (100)	194 (100)	191 (100)	577 (100)
Safety Set [b]	192 (100)	192 (99.0)	186 (97.4)	570 (98.8)
Per-protocol Set [c]	188 (97.9)	184 (94.8)	184 (96.3)	556 (96.4)
Pharmacokinetic Analysis Set [d]	192 (100)[e]	191 (98.5)[f]	0	383 (66.4)

[a] Full Analysis Set includes all patients randomized.
[b] Safety Set includes all patients who received at least one dose of the study drug and had at least one valid post-baseline safety evaluation.
[c] Per-protocol Set includes all patients from the Full Analysis Set without any major protocol deviations and who received at least one dose of study drug.
[d] Pharmacokinetic Analysis Set includes all patients who received at least one dose of encorafenib and/or binimetinib and had at least one evaluable post-baseline encorafenib or binimetinib concentration measurement.
[e] Pharmacokinetic Analysis Set includes 190 patients with samples valid for the specified analyses of encorafenib and 191 patients with samples valid for the specified analyses of binimetinib and AR00426032.
[f] Pharmacokinetic Analysis Set includes 188 patients with samples valid for the specified analyses of encorafenib.

Twenty-one patients (3.6%) were excluded from the PPS (4 patients [2.1%] Combo 450, 10 patients [5.2%] encorafenib, 7 patients [3.7%] vemurafenib). The most common reasons were that patients did not receive at least one dose of study medication or new anti-neoplastic therapy was administered after the start of study treatment and prior to first tumour assessment.

Outcomes and estimation

Primary Endpoint: PFS based on BIRC review in the FAS

PFS for the Combo 450 vs. vemurafenib alone was 14.9 vs. 7.3 months, respectively, with a HR of 0.54 (95% CI 0.41, 0.71, 1 sided stratified log rank p<0.001). No imputations were used for the start or end dates for the primary PFS analysis.

Table 42: Kaplan-Meier Summary of PFS by BIRC – Combo 450 vs. Vemurafenib - (FAS, Part 1)

	Combo 450 N=192	Vemurafenib N=191
Patients with events/Patients included in analysis (%)	98/192 (51.0)	106/191 (55.5)
Percentiles (95% CI) [a]		
25th	7.3 (5.5, 7.5)	3.7 (3.6, 4.0)
50th	14.9 (11.0, 18.5)	7.3 (5.6, 8.2)
75th	25.0 (22.0, NE)	18.5 (12.8, NE)
Event-free probability estimates (95% CI) [b]		
4 months	86.9 (80.9, 91.1)	68.9 (61.1, 75.5)
8 months	65.6 (57.9, 72.2)	42.7 (34.6, 50.6)
12 months	56.7 (48.8, 63.9)	33.4 (25.6, 41.4)
16 months	48.7 (40.6, 56.2)	28.3 (20.7, 36.4)
20 months	38.6 (30.0, 47.1)	23.9 (16.2, 32.3)
24 months	32.3 (22.7, 42.2)	23.9 (16.2, 32.3)

[a] Represents the estimated time (95% CI), in months, at which the specified percentiles occur based on the Kaplan-Meier analysis. The 50th percentile is the same as the median time to event. Values were calculated using the Brookmeyer and Crowley method in PROC LIFETEST.
[b] Estimated probability that a patient will remain event-free up to the specified time point. Event-free probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment groups. Greenwood formula is used for CIs of Kaplan-Meier estimates.

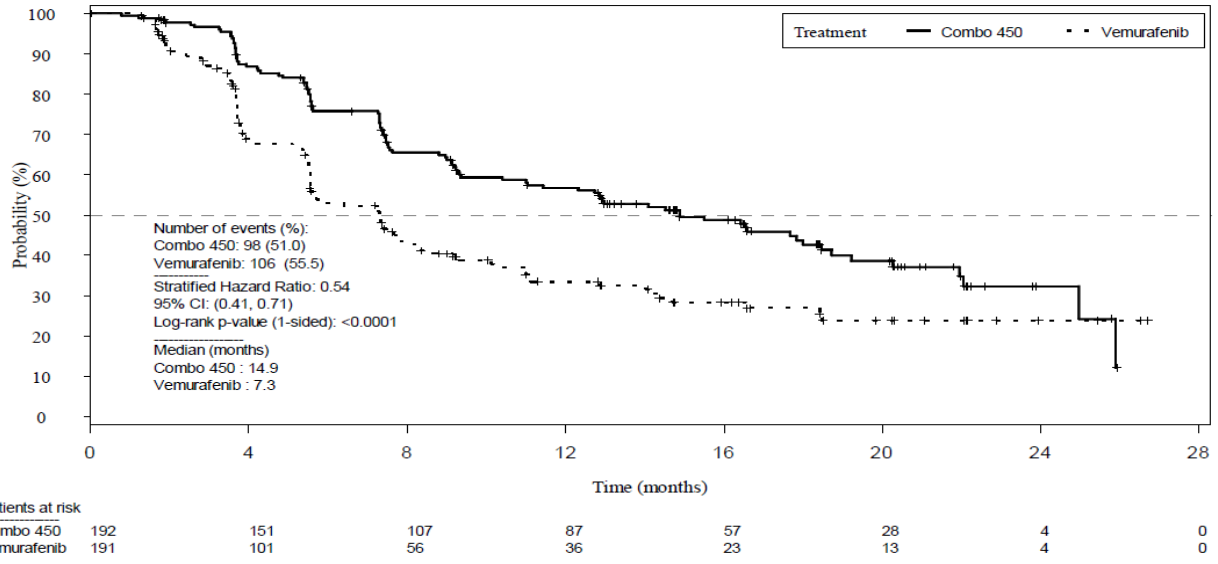


Figure 8: Kaplan-Meier Estimate of PFS Based on BIRC – Combo 450 vs. Vemurafenib (FAS, Part1)

The median PFS values based on Kaplan-Meier estimates were 14.8 months (95% CI 10.4, 18.4) and 7.3 months (95% CI 5.7, 8.5) for the Combo 450 and vemurafenib arms, respectively (HR of 0.49, 95% CI 0.37, 0.64; nominal p < 0.001).

Median follow-up time for PFS per BIRC was 16.7 months for the Combo 450 arm and 14.4 months for the vemurafenib arm. Just under half of the patients were censored for the primary PFS analyis, most prior to the median PFS in each arm. The most common reason for censoring in the Combo 450 and encorafenib arms was because patients remained on treatment (29.7% and 24.2%, respectively), whilst in the vemurafenib arm it was because patients had started a new cancer therapy (19.9%).

Table 43: Reasons for Censoring Patients in the PFS by BIRC – Combo 450 Arm, Encorafenib Arm, Vemurafenib Arm (FAS, Part 1) i.e. Primary & Secondary PFS Analyses

	Combo 450 N=192 n (%)	Encorafenib N=194 n (%)	Vemurafenib N=191 n (%)	Total N=577 n (%)
Number of patients censored	94 (49.0)	98 (50.5)	85 (44.5)	277 (48.0)
Reason for censoring				
Ongoing[a]	57 (29.7)	47 (24.2)	25 (13.1)	129 (22.4)
Lost to follow-up[b]	1 (0.5)	1 (0.5)	0	2 (0.3)
Adequate assessment no longer available[c]	7 (3.6)	2 (1.0)	6 (3.1)	15 (2.6)
Event after 2 or more missed assessments	4 (2.1)	7 (3.6)	1 (0.5)	12 (2.1)
New anti-neoplastic therapy given	18 (9.4)	27 (13.9)	38 (19.9)	83 (14.4)
No baseline assessment	2 (1.0)	2 (1.0)	0	4 (0.7)
No post-baseline assessment	4 (2.1)	11 (5.7)	11 (5.8)	26 (4.5)
Withdrew consent	1 (0.5)	1 (0.5)	4 (2.1)	6 (1.0)

[a] Patients without event and had adequate follow-up as of data cut-off.
[b] Recorded on the End of treatment eCRF, Study evaluation completion eCRF.
[c] Patients censored without adequate evaluations for a specified period (missed 2 scheduled tumour assessments) prior to data cut-off.

Sensitivity analyses

The median PFS by investigator assessment was similar to the BIRC result: 14.8 months (95% CI 10.4, 18.4) vs. 7.3 months (95% CI 5.7, 8.5) for the Combo 450 and vemurafenib arms, respectively, with a HR of 0.49 (95% CI 0.37, 0.64; nominal p < 0.001). In general, there was agreement regarding the type of event (PD/ death) between the Investigator and BIRC. There was discordance regarding the timing of the PD event in about 30% of cases, with no evidence of bias between the arms.

The results in the per protocol set (PPS) by BIRC were reflective of the primary analysis. The median PFS was 15.5 months (95% CI, 11.0, 18.7) in the Combo 450 arm and 7.3 months (95% CI, 5.6, 8.3) in the vemurafenib arm (HR =0.53; 95% CI, 0.40, 0.70; nominal p < 0.001).

Results of additional sensitivity analyses of PFS by BIRC were consistent with the primary PFS analysis, yielding similar HRs (0.53 – 0.56), median PFS values and p values.

These included:

- using unstratified log-rank and Cox regression tests in the FAS
- using stratification factors per the eCRF (per the SAP due to > 5% discordance between randomization strata and eCRF strata)
- "Actual event" including those after ≥2 missing tumour assessments
- "Backdating" events after missing tumour assessments to 8 weeks after the last adequate tumour assessment
- Tumour assessments after initiation of subsequent anticancer therapy

Table 44: Analysis of PFS by BIRC, Sensitivity Analyses (Full Analysis Set, Part 1)

	Median (95% CI) [a]	HR (95% CI)	P value [b]
Primary PFS analysis (FAS)			
Combo 450	**14.9 (11.0, 18.5)**		
Vemurafenib	**7.3 (5.6, 8.2)**	**0.54 (0.41, 0.71)**	**< 0.001**
PFS by eCRF stratification factors			
Combo 450	14.9 (11.0, 18.5)		
Vemurafenib	7.3 (5.6, 8.2)	0.54 (0.41, 0.72)	< 0.001
PFS by "Actual Event" analysis			
Combo 450	14.5 (10.7, 18.0)		
Vemurafenib	7.3 (5.6, 8.2)	0.54 (0.41, 0.72)	< 0.001
PFS by "Backdating" analysis			
Combo 450	14.1 (9.4, 18.0)		
Vemurafenib	7.3 (5.6, 7.9)	0.55 (0.42, 0.72)	< 0.001
PFS by "Further Anticancer Treatment" analysis			
Combo 450	14.9 (11.0, 18.0)		
Vemurafenib	7.3 (5.6, 7.9)	0.53 (0.40, 0.70)	< 0.001

[a] Median (time to event) and its 95% CI are generated by Kaplan-Meier estimation with Brookmeyer & Crowley CI.
[b] p-values are nominal, one-sided and based on the log rank score test. HRs and CIs are derived from the Cox proportional hazards model using the Wald test.

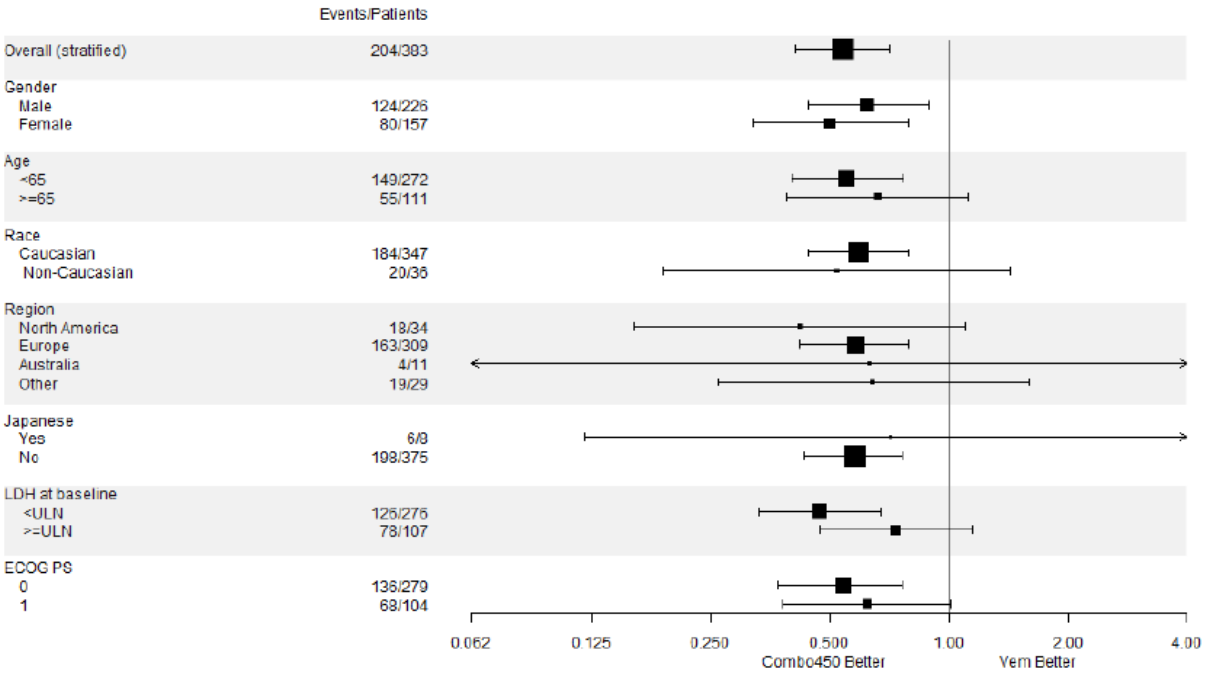
The effect of potential prognostic factors was investigated using a multivariate Cox regression model stratified AJCC stage and ECOG PS.

Table 45: Stratified Multivariate Cox Regression Model of PFS per Central Review with treatment and Other Prognostic Variables as Covariates Encorafenib 450mg + Binimetinib versus Vemurafenib (FAS, Part 1)

Prognostic Variables	Hazard ratio	95% CI	P-value
Full Cox regression model [1]			
Treatment			
Combo 450 vs. Vemurafenib [2]	0.47	(0.35, 0.62)	<0.001
V600 mutation			
V600E vs. V600k	0.83	(0.52, 1.32)	0.430

LDH (increase of 125 IU/L)	1.18	(1.13, 1.24)	<0.001
Gender			
Male vs. Female	1.02	(0.76, 1.37)	0.871
Baseline brain metastases			
Yes vs. No	1.11	(0.48, 2.54)	0.807
Region			0.242
North America vs. Europe	1.67	(1.01, 2.75)	0.047
Australia vs. Europe 0.902	1.07	(0.39, 2.89)	0.902
Other vs. Europe	1.20	(0.70, 2.05)	0.502
Age (increase of 10 years)	1.01	(0.91, 1.13)	0.851

[1] Cox model stratified by IVRS AJCC stage and ECOG performance status.
[2] Hazard Ratio Encorafenib 450mg + Binimetinib versus Vemurafenib. Vemurafenib is the reference group.



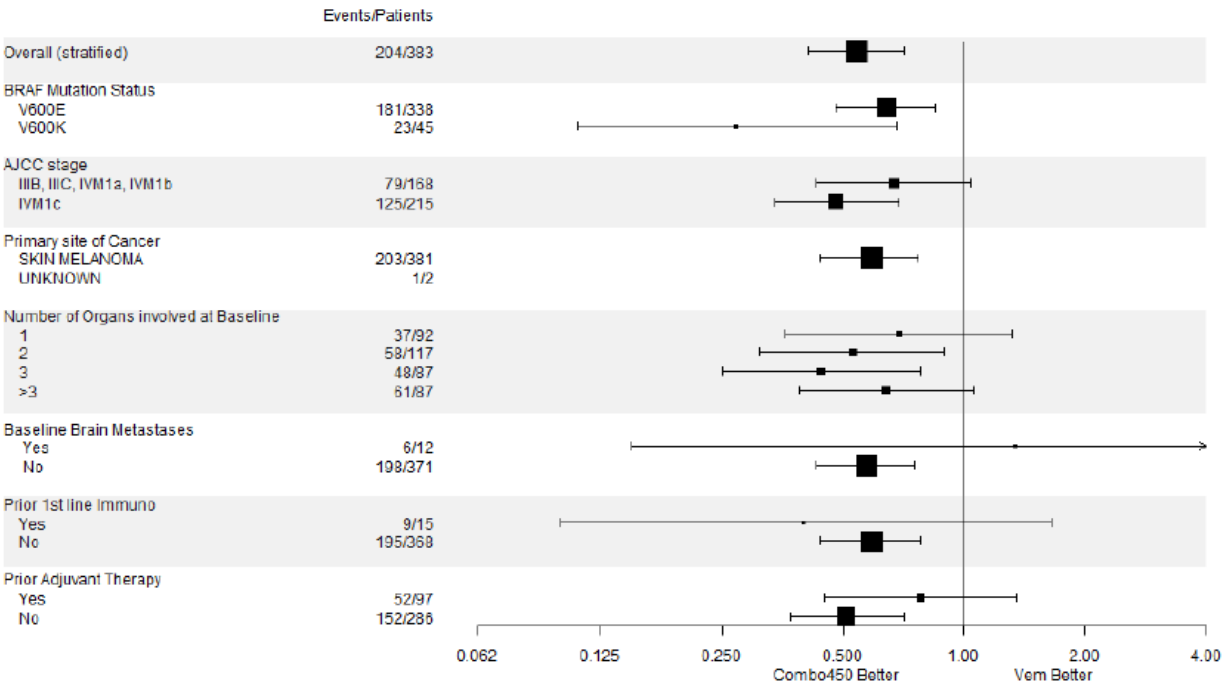


Figure 9: Forest Plot of PFS by BIRC – Combo 450 vs. Vemurafenib (Full Analysis Set, Part 1)

Key Secondary Efficacy Endpoint

PFS Combo 450 vs. Encorafenib

In Part 1, the median PFS was 14.9 months (11.0, 18.5) and 9.6 months (7.5, 14.8) for Combo 450 and encorafenib respectively (HR 0.75, 95% CI 0.56, 1.00). The PFS difference was not statistically significant (p = 0.0256) by the one-sided stratified log-rank test according to the threshold of p < 0.025. Approximately half the patients in each arm had a PFS event (98 patients [51.0%] Combo 450; 96 patients [49.5%] encorafenib). The median follow-up time for PFS per BIRC was 16.7 months for the Combo 450 and 16.6 months for the encorafenib arm.

An updated PFS analysis performed on 07 November 2017 gave a similar result (median PFS: Combo 450 vs encorafenib 14.9 vs 9.6 months, HR: 0.77 (95% CI [0.59-1]), one sided nominal p value=0.0249).

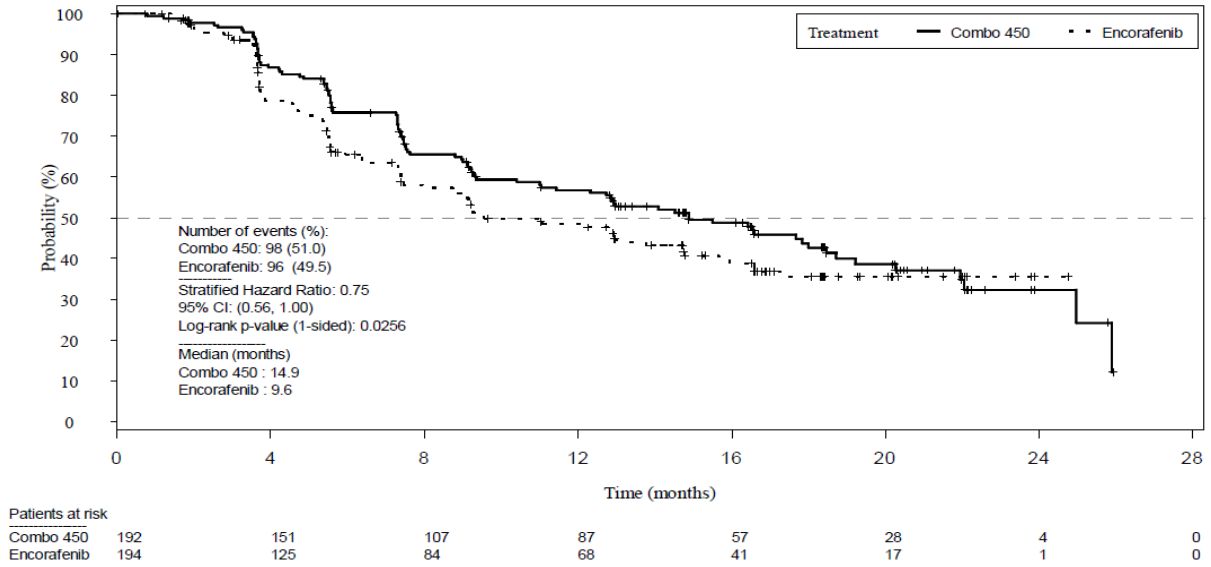


Figure 10: Kaplan-Meier Estimate of PFS Based on BIRC – Combo 450 vs. Encorafenib (FAS, Part 1)

Per Investigator assessment of response, the median PFS estimates were 14.8 months (95% CI 10.4, 18.4) and 9.2 months (95% CI 7.4, 12.9) in the Combo 450 and encorafenib arms, respectively (HR 0.68; 95% CI 0.52, 0.90; nominal p = 0.003). Approximately half the patients in each arm had a PFS event (102 [53.1%] Combo 450; 108 [55.7%] encorafenib).

Sensitivity analyses of PFS by BIRC using data from the FAS were conducted as per the primary efficacy endpoint.

The HR for PFS of Combo 450 vs. encorafenib using unstratified log-rank and Cox regression tests was 0.81 (95% CI 0.61, 1.07; nominal p = 0.0714).

The remaining sensitivity analyses yielded nominal p values <0.025 (see Table below).

Table 46: Analysis of PFS by BIRC, Sensitivity Analyses of Secondary Endpoint (FAS, Part 1)

	Median (95% CI) [a]	HR (95% CI) [b]	P value [c]
Secondary PFS analysis (FAS)			
Combo 450	**14.9 (11.0, 18.5)**		
Encorafenib	**9.6 (7.5, 14.8)**	**0.75 (0.56, 1.00)**	**0.0256**
PFS by eCRF stratification factors			
Combo 450	14.9 (11.0, 18.5)		
Encorafenib	9.6 (7.5, 14.8)	0.73 (0.55, 0.98)	0.0173
PFS by "Actual Event" analysis			
Combo 450	14.5 (10.7, 18.0)		
Encorafenib	9.6 (7.5, 13.8)	0.74 (0.56, 0.98)	0.0190
PFS by "Backdating" analysis			
Combo 450	14.1 (9.4, 18.0)		
Encorafenib	9.3 (7.4, 12.9)	0.74 (0.56, 0.98)	0.0166
PFS by "Further Anticancer Treatment" analysis			
Combo 450	14.9 (11.0, 18.0)		
Encorafenib	9.5 (7.5, 13.0)	0.72 (0.55, 0.96)	0.0114

Table 47: Unstratified Cox Regression Model for PFS per Central Review by Subgroup (FAS, Part 1)

	Event /N (%)	Median Time (95% CI) (months) [2]	Cox Model [1]	
			Hazard Ratio	95% CI
All Subjects				
Combo 450	98/192 (51.0)	14.9 (11.0, 18.5)		
Encorafenib [3]	96/194 (49.5)	9.6 (7.5, 14.8)	0.81	(0.61, 1.07)
Vemurafenib [4]	106/191 (55.5)	7.3 (5.6, 8.2)	0.58	(0.44, 0.77)
AJCC stage				
IIIB, C, IVM1a, b				
Combo 450	37/ 84 (44.0)	17.8 (11.4, NE)		
Encorafenib [3]	36/ 84 (42.9)	16.6 (9.2, NE)	0.97	(0.61, 1.53)
Vemurafenib [4]	42/ 84 (50.0)	11.0 (7.3, 14.7)	0.67	(0.43, 1.04)
IVM1c				
Combo 450	61/108 (56.5)	13.0 (7.5, 18.0)		
Encorafenib [3]	60/110 (54.5)	7.4 (5.5, 12.8)	0.68	(0.47, 0.98)
Vemurafenib [4]	64/107 (59.8)	5.6 (3.8, 7.3)	0.48	(0.34, 0.69)
ECOG PS				
ECOG PS =0				
Combo 450	63/139 (45.3)	17.7 (12.3, 25.9)		
Encorafenib [3]	65/143 (45.5)	13.0 (9.2, 17.3)	0.83	(0.58, 1.17)
Vemurafenib [4]	73/140 (52.1)	7.3 (5.6, 10.1)	0.54	(0.38, 0.76)
ECOG PS =1				
Combo 450	35/ 53 (66.0)	11.0 (5.6, 16.6)		
Encorafenib [3]	31/ 51 (60.8)	5.5 (3.7, 9.1)	0.70	(0.43, 1.15)
Vemurafenib [4]	33/ 51 (64.7)	7.3 (3.6, 8.6)	0.62	(0.38, 1.01)
Prior first-line immunotherapy				
Yes				
Combo 450	5/ 8 (62.5)	11.4 (3.7, NE)		
Encorafenib [3]	5/ 11 (45.5)	5.6 (1.4, NE)	0.81	
Vemurafenib [4]	4/ 7 (57.1)	5.6 (3.8, 8.3)	0.40	(0.10, 1.64)
No				
Combo 450	93/184 (50.5)	14.9 (11.0, 18.7)		
Encorafenib [3]	91/183 (49.7)	11.0 (8.0, 14.8)	0.81	(0.60, 1.08)
Vemurafenib [4]	102/184 (55.4)	7.3 (5.6, 8.6)	0.59	(0.44, 0.78)
Prior adjuvant immunotherapy				
Yes				
Combo 450	27/ 49 (55.1)	15.5 (9.1, 25.0)		
Encorafenib [3]	23/ 47 (48.9)	12.8 (5.6, NE)	0.80	(0.45, 1.40)
Vemurafenib [4]	25/ 48 (52.1)	11.1 (5.5, NE)	0.78	(0.45, 1.35)
No				
Combo 450	71/143 (49.7)	14.9 (10.4, 18.7)		
Encorafenib [3]	73/147 (49.7)	9.6 (7.4, 15.7)	0.82	(0.59, 1.13)
Vemurafenib [4]	81/143 (56.6)	7.3 (5.6, 7.7)	0.51	(0.37, 0.71)
BRAF Mutation Status				
V600E				
Combo 450	90/170 (52.9)	14.9 (10.4, 18.5)		
Encorafenib [3]	87/173 (50.3)	11.0 (8.0, 14.8)	0.86	(0.64, 1.15)
Vemurafenib [4]	91/168 (54.2)	7.4 (5.6, 9.2)	0.64	(0.48, 0.85)
V600K				
Combo 450	8/ 22 (36.4)	NE (7.5, NE)		
Encorafenib [3]	8/ 19 (42.1)	9.2 (3.7, NE)	0.53	(0.20, 1.44)
Vemurafenib [4]	15/ 23 (65.2)	5.5 (3.7, 12.8)	0.27	(0.11, 0.68)

[1] Cox PH model are unstratified.
[2] Median (time to event) and its 95% CI are generated by KM estimation.
[3] Analyses comparing Combo 450 versus Encorafenib (Part 1) only consider data from patients randomized to those treatment groups. Hazard ratio Combo versus Encorafenib. Encorafenib is the reference group.
[4] Analyses comparing Combo 450 versus Vemurafenib only consider data from patients randomized to those treatment groups. Hazard ratio Combo 450 versus Vemurafenib. Vemurafenib is the reference group.

Overall 103 out of the 577 (17.9%) patients randomised in the CMEK162B2301 study changed therapy before progression. Of these 103, 44 (42.7%) were followed until progression or death (death as first event, all due to study indication): 9 (37.5%), 14 (42.4%) and 21 (45.7%) in the Combo 450, Enco 300 and vemurafenib arms respectively.

Table 48: Outcomes of patients who received a new anticancer treatment before progression, death [CMEK162B2301, FAS (Part 1)]

Outcomes after change of therapy[a]	**Encorafenib 450mg + Binimetinib N=24 n (%)**	**Encorafenib N=33 n (%)**	**Vemurafenib N=46 n (%)**
Progression	1 (4.2)	9 (27.3)	4 (8.7)
Death	8 (33.3)	5 (15.2)	17 (37.0)
Censored	15 (62.5)	19 (57.6)	25 (54.3)
No baseline assessment	*2 (8.3)*	*0*	*0*
No post-baseline assessment	*1 (4.2)*	*4 (12.1)*	*4 (8.7)*
Adequate assessment no longer available	*10 (41.7)*	*12 (36.4)*	*16 (34.8)*
Withdrew Consent	*0*	*1 (3.0)*	*3 (6.5)*
Lost to Follow-up	*0*	*1 (3.0)*	*0*
Ongoing	*2 (8.3)*	*1 (3.0)*	*2 (4.3)*

To fufil the EMA guidelines definition, three additional sensitivity analyses were performed as requested during the procedure. These supported the results of the initial analysis with regards to Combo 450 vs vemurafenib (primary objective) and Combo 450 vs encorafenib 300mg QD (key secondary objective).

Table 49: Stratified Cox Regression Model of Progression Free Survival per Central Review - Sensitivity analysis [CMEK162B2301, FAS]

	Event N(%)	Median (95% CI) (month)	Survival (%) at 24 months	P value	HR (95% CI)
Primary analysis[1]					
Encorafenib 450mg + Binimetinib	98/192 (51.0)	14.9 (11.0, 18.5)	32.3 (22.7, 42.2)		
Encorafenib[a]	96/194 (49.5)	9.6 (7.5, 14.8)	35.5 (27.5, 43.7)	0.0513	0.75 (0.56 - 1.00)
Vemurafenib[b]	106/191 (55.5)	7.3 (5.6, 8.2)	23.9 (16.2, 32.3)	<.0001	0.54 (0.41 - 0.71)
'Objective event (EMA recommendation)' sensitivity analysis[2]					
Encorafenib 450mg + Binimetinib	112/192 (58.3)	14.1 (10.7, 16.6)	27.5 (18.9, 36.9)		
Encorafenib[a]	118/194 (60.8)	9.3 (7.4, 12.3)	29.5 (22.4, 36.9)	0.0181	0.73 (0.56 - 0.95)
Vemurafenib[b]	129/191 (67.5)	7.3 (5.6, 8.6)	17.6 (11.4, 24.9)	<.0001	0.56 (0.43 - 0.72)
'Change of therapy and withdrawal included as events' sensitivity analysis[3]					
Encorafenib 450mg + Binimetinib	128/192 (66.7)	10.7 (9.1, 13.0)	24.8 (17.0, 33.4)		
Encorafenib[a]	144/194 (74.2)	7.2 (5.6, 9.1)	22.2 (15.9, 29.2)	0.0018	0.68 (0.53 - 0.87)
Vemurafenib[b]	161/191 (84.3)	5.6 (4.4, 6.1)	12.7 (8.1, 18.2)	<.0001	0.48 (0.38 - 0.61)
'Push back censoring' sensitivity analysis[4]					
Encorafenib 450mg + Binimetinib	112/192 (58.3)	16.4 (12.3, 19.2)	36.6 (28.4, 44.7)		
Encorafenib[a]	118/194 (60.8)	11.8 (9.1, 14.8)	37.9 (30.9, 44.9)	0.1317	0.82 (0.63 - 1.06)
Vemurafenib[b]	129/191 (67.5)	8.2 (7.2, 11.0)	31.0 (24.3, 37.9)	0.0017	0.67 (0.52 - 0.86)

[1] Primary analysis uses censoring of events occurring after 2 or more missing tumour assessments or change of therapy
[2] 'Objective event' analysis includes the event (progressive disease or death) whenever it occurs even after 2 or more missing tumour assessments, withdrawal or new anticancer therapy.
[3] 'Change of therapy and withdrawal included as events' analysis considers as events progression and death as well as change of therapy or withdrawal whichever occurs the first
[4] 'Push back censoring' analysis includes the event (progressive disease or death) whenever it occurs and censored patients at the clinical cut-off date.

Other Secondary Efficacy Endpoints

PFS, Encorafenib vs. Vemurafenib

Analysis of the PFS by BIRC of encorafenib vs. vemurafenib treatment showed a difference of approximately 2.3 months (9.6 months vs. 7.3 months; nominal one-sided log-rank p = 0.004; HR = 0.68, 95% CI 0.52, 0.90). Investigator assessment of response gave similar PFS durations (encorafenib 9.2 months, vemurafenib 7.3 months; nominal one-sided log-rank p = 0.004; HR = 0.68, 95% CI 0.52, 0.90). Median PFS values by BIRC were the same in the PPS as in the FAS.

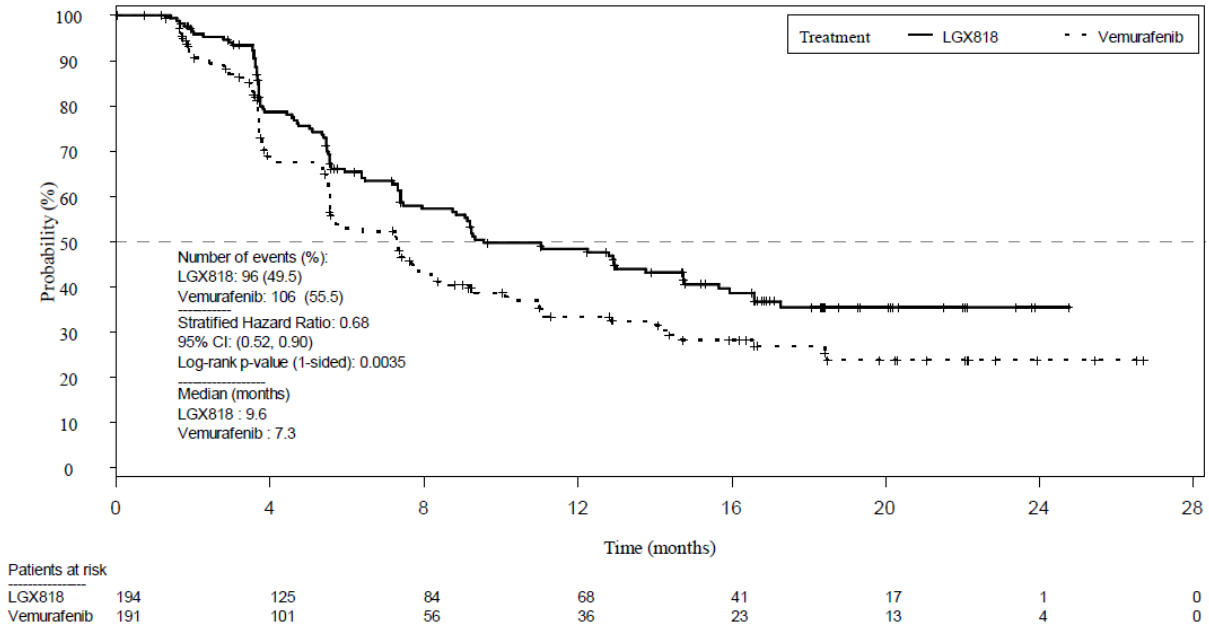


Figure 11: Kaplan-Meier Estimate of PFS Based on BIRC Assessment –Encorafenib vs. Vemurafenib (FAS, Part 1)

Objective Response Rate and Disease Control Rate

Table 50: Best Overall Response by BIRC (FAS, Part 1)

	Combo 450 N=192 n (%)	Encorafenib N=194 n (%)	Vemurafenib N=191 n (%)
Patients with measurable disease at baseline[a]	175 (91.1)	180 (92.8)	183 (95.8)
Patients with non-measurable disease only at baseline[a]	15 (7.8)	12 (6.2)	8 (4.2)
Confirmed ORR: CR + PR	121 (63.0)	98 (50.5)	77 (40.3)
95% CI	(55.8, 69.9)	(43.3, 57.8)	(33.3, 47.6)
Confirmed BOR[b,c]			
CR	15 (7.8)	10 (5.2)	11 (5.8)
PR	106 (55.2)	88 (45.4)	66 (34.6)
Stable disease	46 (24.0)	53 (27.3)	73 (38.2)
Non-CR/Non-PD[d]	10 (5.2)	12 (6.2)	6 (3.1)
PD	2 (1.0)	6 (3.1)	13 (6.8)
DCR: CR+PR+stable disease+ Non-PD/Non-CR	177 (92.2)	163 (84.0)	156 (81.7)
95% CI[e]	(87.4 , 95.6)	(78.1 , 88.9)	(75.4 , 86.9)
Unknown[f]	11 (5.7)	25 (12.9)	22 (11.5)
Not Assessed[g]	2 (1.0)	0	0

[a] Does not include the 2 patients who were not assessed by BIRC.
[b] Best overall response is based on central reviewer's assessment using RECIST v1.1.
[c] CR and PR are confirmed by repeat assessments performed not less than 4 weeks after the criteria for response is first met.
[d] Non-CR/non-PD applies only to patients with non-target lesions at baseline who did not achieve a CR or have PD.
[e] The 95% CI for the frequency distribution of each variable were computed using Clopper-Pearson's method.

[f] Unknown response: Not included in BOR assessment but included in denominator for ORR and DCR. Progression has not been documented and one or more lesions have not been assessed or have been assessed using a different method than baseline. See Table 14.2-3.2a for reasons for unknown status.
[g] Not included in BOR assessment but included in denominator for ORR and DCR. No assessment has occurred by BIRC; not included in patients with measurable or non-measurable disease at baseline.

Median time to objective response (TTR) per BIRC, calculated for responding patients only (confirmation not required), was 1.9 months in the Combo 450 arm (95% CI 1.9, 1.9), 2.0 months in the encorafenib arm (95% CI 1.9, 3.6) and 2.1 months in the vemurafenib arm (95% CI 1.9, 3.7). Median TTR per Investigator assessment was also approximately 2 months for each arm. This timing corresponded with the first post-baseline response assessment at Cycle 3 Day 1.

Kaplan-Meier estimates of median duration of response (DOR) per BIRC, calculated for confirmed responses, were 16.6 months in the Combo 450 arm (95% CI 12.2, 20.4; range 1.64 – 22.11), 14.9 months in the encorafenib arm (95% CI 11.1, NE; range 0.62 – 15.47) and 12.3 months in the vemurafenib arm (95% CI 6.9, 16.9; range 0.92 – 16.89).

Investigator review revealed a similar pattern but a higher ORR in each arm (75.0 % [95% CI 68.3, 81.0]; 57.7% [95% CI 50.4, 64.8]; 49.2 % [95% CI 41.9, 56.5], respectively).

The confirmed CR by Investigator review was higher than by BIRC (16.1%, 8.8% and 7.3% of patients in the Combo 450, encorafenib and vemurafenib arms, respectively) and their median time to CR was 5.5 months, 5.5 months and 3.9 months, respectively.

The DCR per Investigator review was similar to per BIRC.

Median TTR per Investigator assessment was also approximately 2 months for each arm. This timing corresponded with the first post-baseline response assessment at Cycle 3 Day 1.

Kaplan-Meier estimates of median DOR per Investigator, calculated for confirmed responses, were similar to those by BIRC: 16.2 months, 14.8 months and 8.4 months in the Combo 450, encorafenib and vemurafenib arms.

Overall Survival, Combo 450 vs. Vemurafenib

As of the data cut-off (7 November 2017), 80 patients (13.9%) were ongoing in the treatment period of the study (22.4% Combo 450 arm, 12.4% encorafenib arm, 6.8% vemurafenib arm). The median duration of exposure to study treatment in the Combo 450 arm (11.8 months) was longer than in the encorafenib (7.2 months) and vemurafenib (6.1 months) arms. Within the Combo 450 arm, median durations of exposure to encorafenib and binimetinib were identical (11.8 months).

The most common reason for discontinuation from study treatment, in all arms, was progressive disease and the rate was higher in the vemurafenib arm (57.1%) as compared with the Combo 450 (51.6%) and encorafenib (51.5%) arms. The rates of withdrawal by physician and by patients were higher for vemurafenib (8.9% each) and encorafenib (12.4% and 8.8%) vs Combo 450 (4.7% and 5.7%). The proportion of patients censored for this OS analysis in the Combo 450 arm (45.3%) was higher than that observed in the vemurafenib arm (33.5%). Most censored patients in both groups who were alive and ongoing had a last contact within the 12 weeks prior to data cut-off.

For all randomized patients, the median time between randomisation and OS cut-off dates was 37.45 months [30.98–46.29 months]. When measured as the time from randomisation until event/censoring, the median potential follow-up duration using reverse Kaplan Meier for OS was 37.2 months in the Combo 450 arm, 36.3 months in the encorafenib arm and 35.9 months in the vemurafenib arm.

A lower proportion of patients in the Combo 450 arm (41.7%) received antineoplastic therapy after discontinuation of study treatment compared with the encorafenib (55.7%) and vemurafenib (62.3%) arms, partly due to a higher proportion of patients in the Combo 450 arm who continued to receive study treatment as of the data cut-off. A similar proportion of patients in each arm received subsequent treatment with a monoclonal antibody, mainly checkpoint inhibitors (34.4% Combo 450, 36.1% encorafenib, 39.8% vemurafenib arm). A lower proportion of patients in the Combo 450 arm (10.9%) received subsequent treatment with BRAF inhibitors and/or combinations of BRAF and MEK inhibitors after discontinuation of study treatment as compared with either the encorafenib (21.6 %) or the vemurafenib (32.9%) arms.

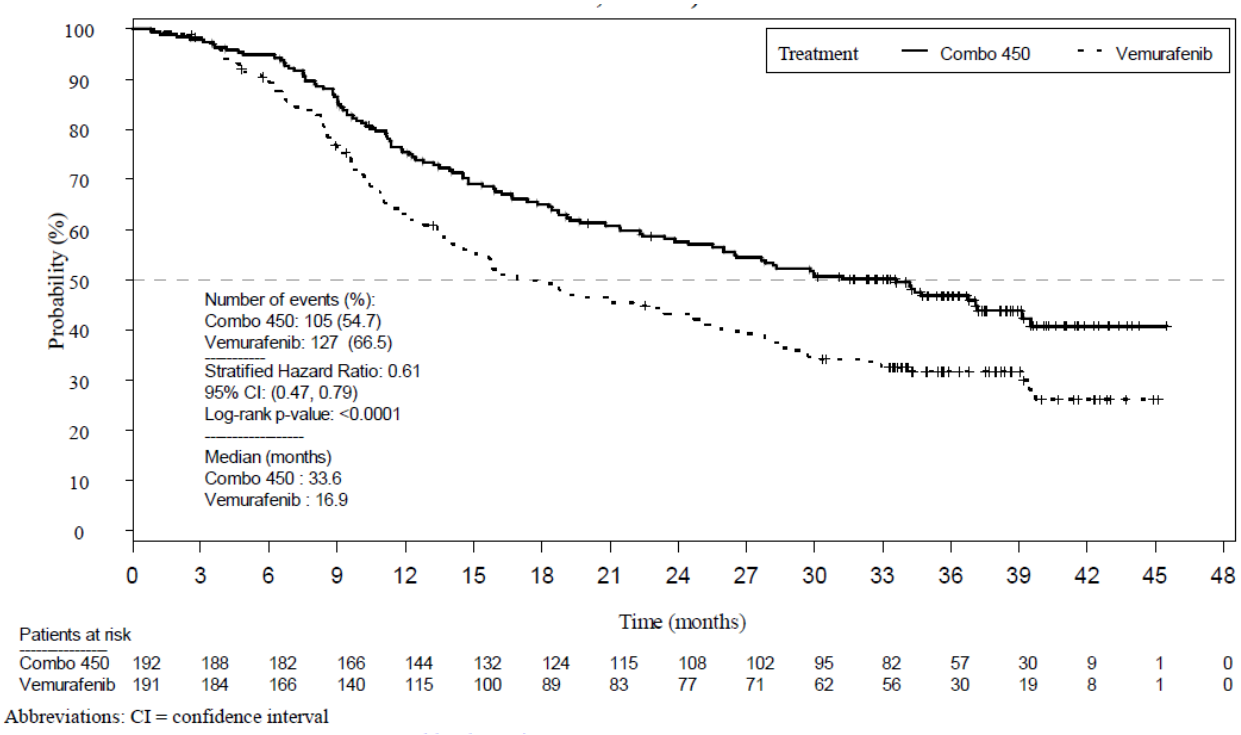


Figure 12: Kaplan-Meier Plot of Overall Survival, Combo 450 vs. Vemurafenib (Full Analysis Set, Part 1)

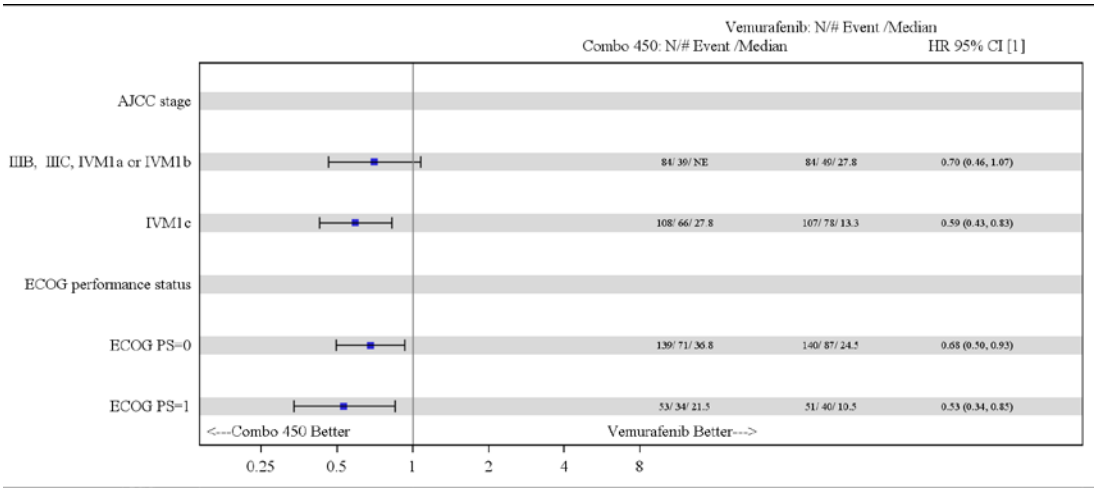
An estimated 39% reduction in the risk of death was observed for patients treated with Combo 450 compared to those treated with vemurafenib (HR 0.61, 95% CI 0.47, 0.79), with median OS values of 33.6 months (95% CI 24.4, 39.2) and 16.9 months (95% CI 14.0, 24.5), respectively.

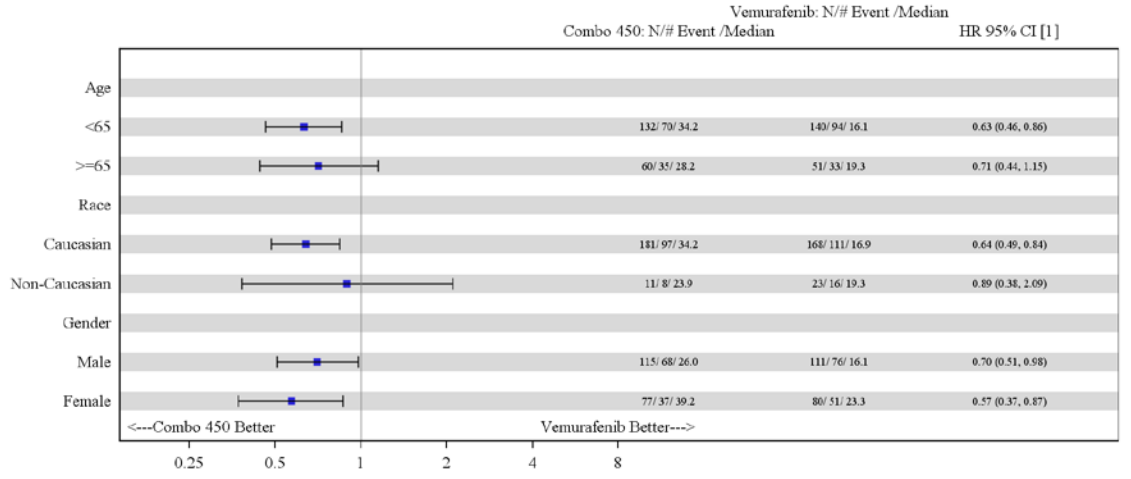
Estimates of OS at 12 months and 24 months were 75.5% (95% CI 68.8, 81.0) and 57.6% (95% CI 50.3, 64.3) for Combo 450 compared to 63.1% (95% CI 55.7, 69.6) and 43.2% (95% CI 35.9, 50.2) for vemurafenib.

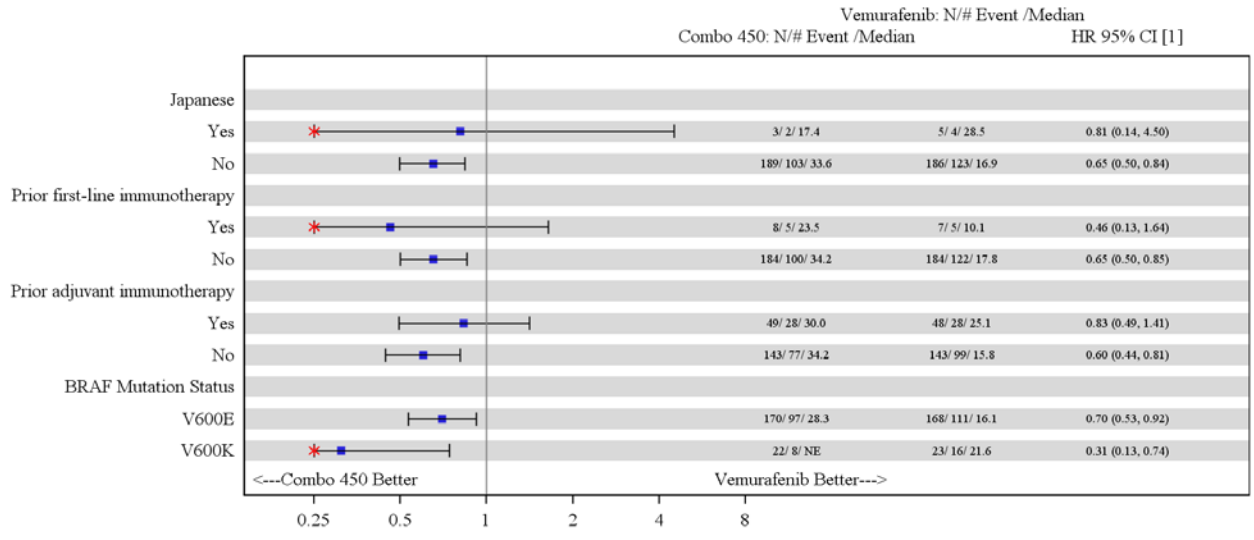
The results of sensitivity analyses are consistent with those of the interim OS analysis and lead to similar conclusions about treatment effect.

A multivariate Cox regression model stratified by the study stratification factors was used to explore the robustness of the statistical significance of treatment effect on OS when adjusting for main prognostic factors. The only other prespecified covariate that reached statistical significance was LDH, which was associated with an increase in the relative risk of death which was associated with an

increase in the relative risk of death (HR 1.21; 95% CI 1.16, 1.27; p < 0.001, 2-sided) for each 125 IU/L increase in LDH.







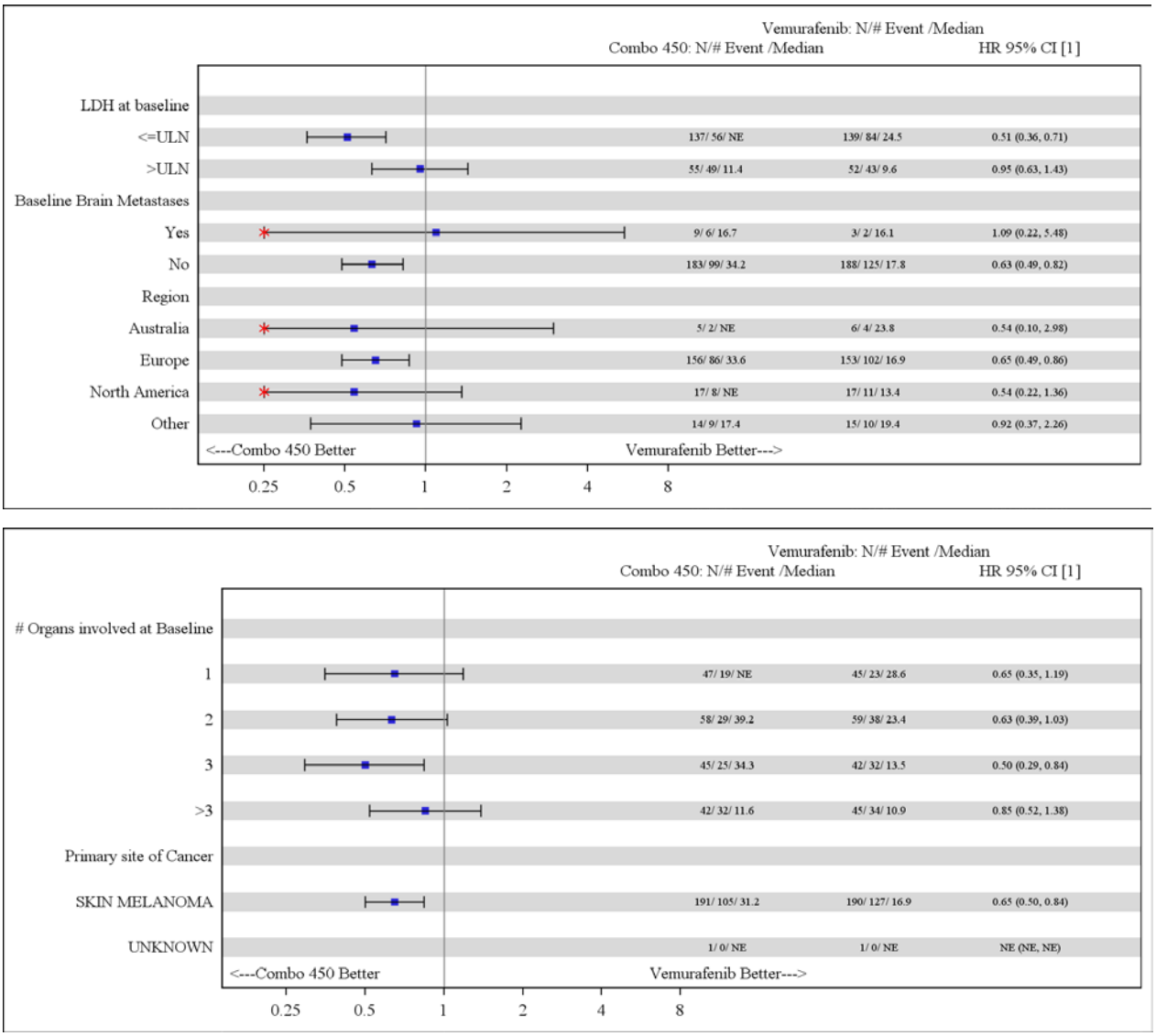
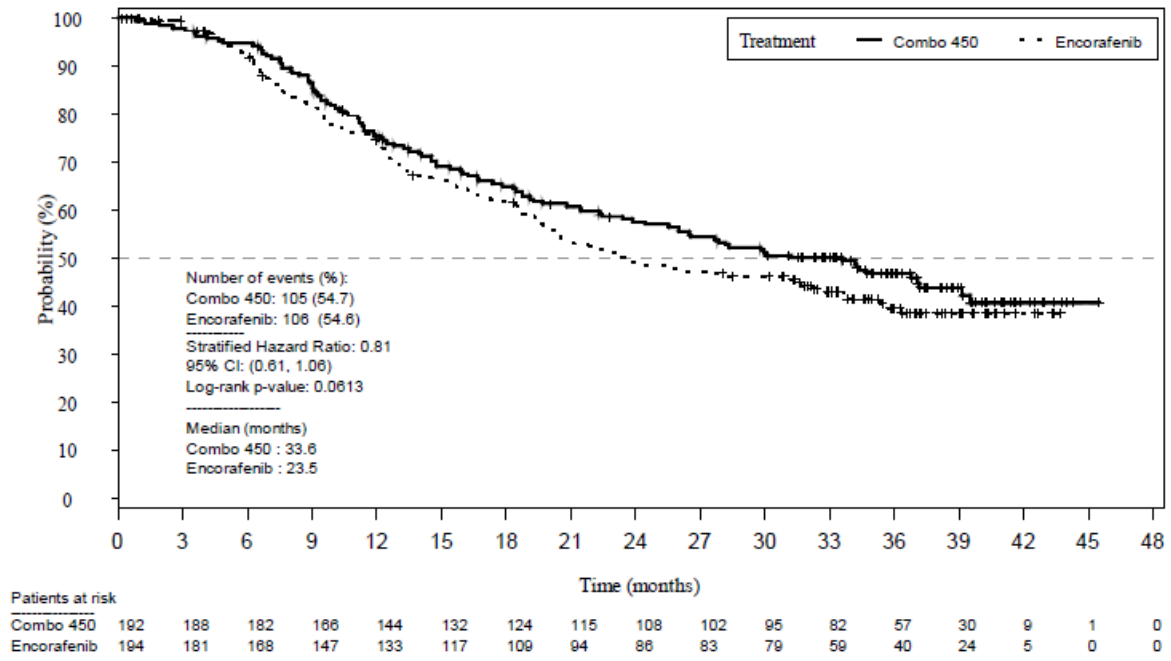


Figure 13: Forest Plot of Hazard Ratio with 95% Confidence Interval for Overall Survival from Subgroup Analysis Encorafenib 450mg+Binimetinib versus Vemurafenib (Full Analysis Set, Part 1)

Overall Survival, Combo 450 vs. Encorafenib

Median OS values for Combo 450 and encorafenib were 33.6 months (24.4, 39.2) and 23.5 months (19.6, 33.6) respectively (HR 0.81, 95% CI 0.61, 1.06, nominal p value =0.0613, 2-sided).



Abbreviations: CI = confidence interval

Figure 14: Kaplan-Meier Plot of Overall Survival, Combo 450 vs. Encorafenib (Full Analysis Set, Part 1)

Estimates of OS at 12 months and 24 months were 75.5% (68.8, 81.0) and 57.6% (50.3, 64.3) for Combo 450 compared to 74.6% (67.6, 80.3) and 49.1% (41.5, 56.2) for encorafenib.

A multivariate Cox regression model stratified by the study stratification factors was used to explore the robustness of the statistical significance of treatment effect on OS when adjusting for main prognostic factors. The only other prespecified covariate that reached statistical significance was LDH, which was associated with an increase in the relative risk of death (HR 1.21; 95% CI 1.16, 1.27; p < 0.001, 2-sided) for each 125 IU/L increase in LDH. All unstratified subgroup analyses demonstrated median OS point estimates in favour of the Combo 450 arm except for Japanese patients (6 patients in total) and Region Other (27 patients in total) and > 3 organs involved at baseline (66 patients in total).

Overall Survival, Encorafenib vs. Vemurafenib

The median OS was 23.5 months (95% CI 19.6, 33.6) and 16.9 months (95% CI 14.0, 24.5), respectively, for patients treated with encorafenib compared with vemurafenib with a HR 0.76 (95% CI 0.58, 0.98). Estimates of OS at 12 months and 24 months were 74.6% (67.6, 80.3) and 49.1% (41.5, 56.2) for encorafenib compared to 63.1% (55.7, 69.6) and 43.2% (35.9, 50.2) for vemurafenib.

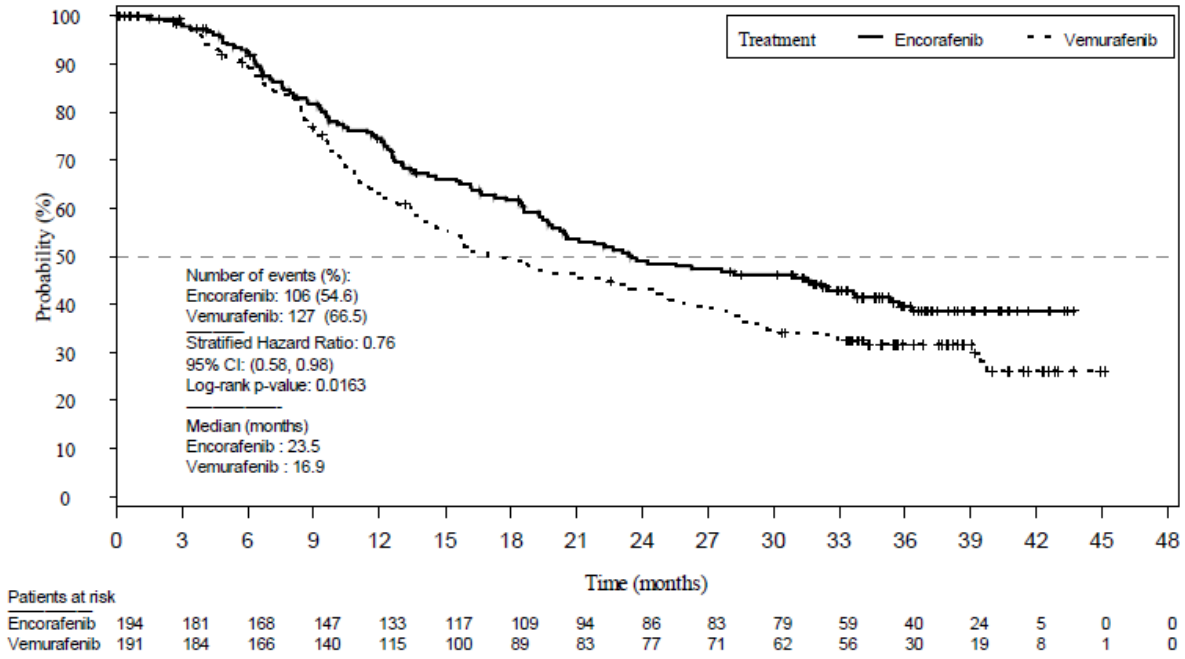


Figure 15: Kaplan-Meier Plot of Overall Survival, Encorafenib vs. Vemurafenib (Full Analysis Set, Part 1)

The data cut-off date for the ***OS analysis reviewed by the DMC*** was 19 May 2016, by which time a total of 157 OS events were observed in the Combo 450 and vemurafenib arms combined in Part 1 of the study.

For patients treated with Combo 450, median OS value was 26.0 months compared to 16.9 months for those treated with vemurafenib (HR 0.58, 95% CI 0.42, 0.80. Confidence intervals were not provided.

For patients treated with Combo 450 compared to those treated with encorafenib (HR 0.77, 95% CI 0.55, 1.08), median OS values were 26.0 months and 23.5 months, respectively.

Table 51: Study CMEK162B2301, Part 1: Overall survival interim results (cut-off date: 7 November 2017)

	Encorafenib + binimetinib N=192 (Combo 450)	**Encorafenib N=194 (Enco 300)**	**Vemurafenib N=191 (Vem)**
OS			
Number of events (%)	105 (54.7)	106 (54.6)	127 (66.5)
Median, months (95% CI)	33.6 (24.4, 39.2)	23.5 (19.6, 33.6)	16.9 (14.0, 24.5)
Survival at 12 months (95% CI)	75.5% (68.8, 81.0)	74.6% (67.6, 80.3)	63.1% (55.7, 69.6)
Survival at 24 months (95% CI)	57.6% (50.3, 64.3)	49.1% (41.5, 56.2)	43.2% (35.9, 50.2)
HR (95% CI) (vs Vem) p-value (stratified log-rank)	0.61 (0.47, 0.79) <0.0001		
HR (95% CI) (vs Enco 300) p-value (stratified log-rank)	0.81 (0.61,1.06) 0.061		

Health related Quality of Life (HRQoL) Analyses

Patient compliance with the 3 QoL instruments (FACT-M, EORTC-QLQ-C30, EQ-5D-5L) was calculated for patients still "at-risk" i.e. receiving treatment or in post-treatment follow-up on the protocol-scheduled PRO assessment date. Compliance with the 3 questionnaires was equivalent among the 3 treatment arms, with approximately 80%-95% of patients still at risk completing the assessment from baseline to Cycle 25.

At baseline, the mean [SD] **FACT-M** score was similar in the 3 treatment arms: Combo 450 (52.39 [9.05]), Enco 300 (52.84 [8.23]) and vemurafenib arm (52.01 [8.65]). The median time to definitive 10% deterioration in the FACT-M global health status score was not reached in the Combo 450 arm (95% CI 22.1, NE) and was 22.1 months (95% CI 15.2, NE) in the vemurafenib arm with a HR for the difference of 0.46 (95% CI 0.29, 0.72) using a stratified Cox regression model. The median time to definitive 10% deterioration in the FACT-M was 20.3 months (95% CI 15.0, NE) in the encorafenib arm with a HR for the difference between Combo 450 and encorafenib of 0.48 (95% CI 0.31, 0.75) using a stratified Cox regression model.

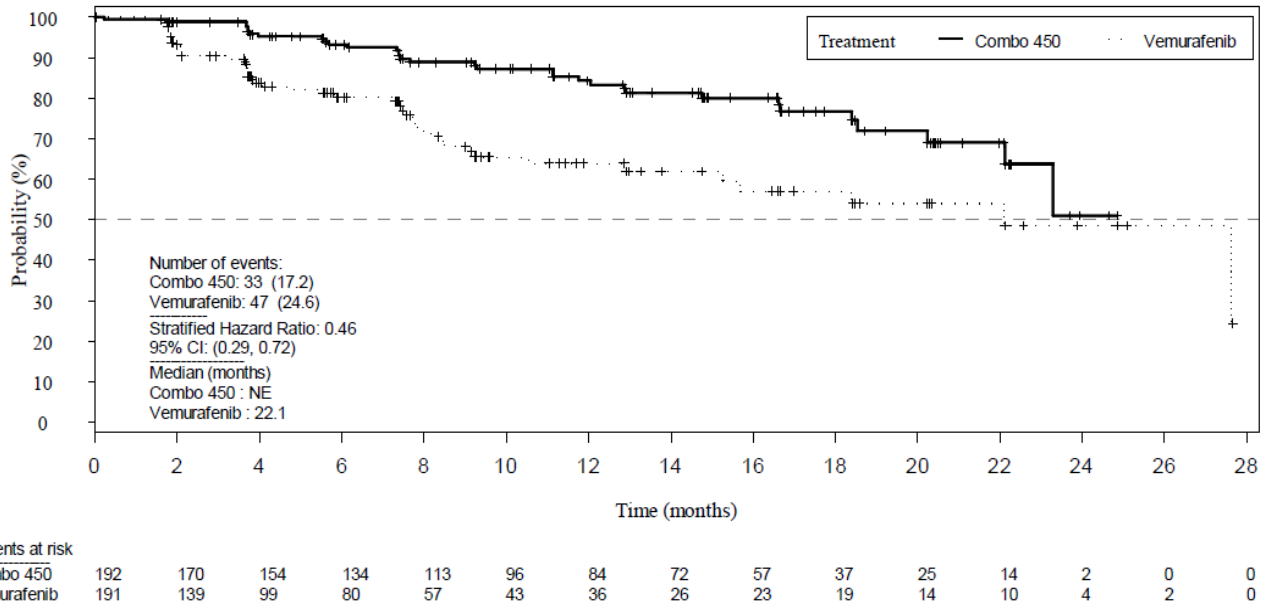


Figure 16: Kaplan-Meier Plot of Time to Definitive 10% Deterioration in FACT-M Global Health Status – Combo 450 vs. Vemurafenib (FAS, Part 1)

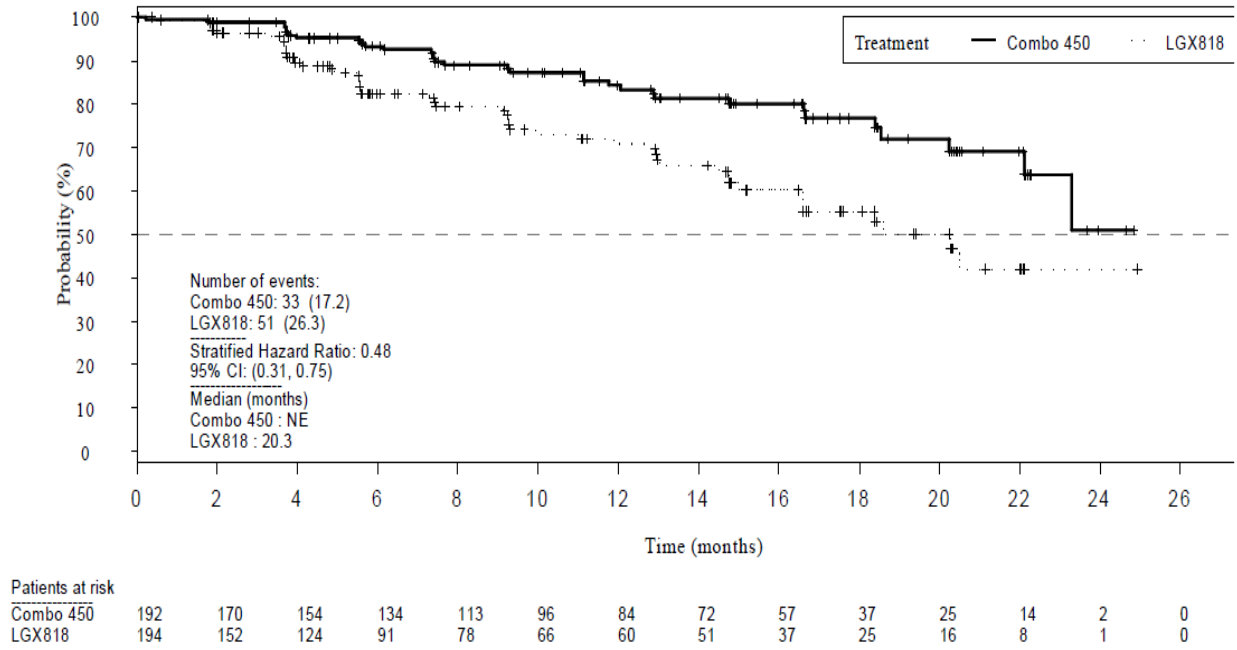


Figure 17: Kaplan-Meier Plot of Time to Definitive 10% Deterioration in FACT-M Global Health Status – Combo 450 vs. Enco 300 (FAS, Part1)

At baseline, the mean [SD] **EORTC QLQ-C30 global health status** score was similar in the 3 treatment arms: Combo 450 (66.72 [21.59]), Enco 300 (66.10 [21.16]) and the vemurafenib arm (64.74 [23.61]). The median time to definitive 10% deterioration in the EORTC QLQ-C30 global health status score was delayed by more than 7 months in the Combo 450 arm compared to the vemurafenib arm: 23.9 months (95% CI 20.4, NE) vs. 16.6 months (95% CI 11.9, NE) with a HR for the difference of 0.55 (95% CI 0.37, 0.80) using a stratified Cox regression model. The median time to definitive 10% deterioration in the QLQ-C30 global health status scores was longer in the Combo 450 arm compared with the Enco 300 arm (14.7 months [95% CI 9.2, 18.4]), with a HR for the difference of 0.45 (95% CI 0.31, 0.65) using a stratified Cox regression model.

At baseline, the mean **EQ-5D-5L** index score was similar for each arm (Combo 450 = 0.74, encorafenib = 0.76, vemurafenib = 0.73) and the median was 0.77 for each of the 3 treatment arms. The Combo 450 arm showed a slight improvement at Cycle 3 Day 1 from baseline and the vemurafenib showed no change. In subsequent visits, the scores decreased over time for both arms. Comparison of the Combo 450 arm vs. the encorafenib arm showed similar results to the comparison of the Combo 450 arm and vemurafenib arm.

Study CMEK162B2301 PART 2

The main objective of Part 2 (a key secondary objective) was to further quantify the contribution of binimetinib to the combination of encorafenib and binimetinib, by comparing PFS of Combo 300 (encorafenib 300 mg QD and binimetinib 45 mg BID) vs. encorafenib single-agent (encorafenib 300 mg QD).

Approximately 320 patients were planned to be randomised in a 3:1 ratio to Combo 300: Enco 300. The inclusion – exclusion criteria were identical to Part 1.

Statistical Methods for Efficacy Analyses in the Part 2 CSR (Combo 300 vs. Enco 300)

An unplanned initial analysis of Part 2 based on 293 events (vs 340 events planned) was performed using a data cut-off date of 09 November 2016 in agreement with the FDA. Analysis of the Part 1 key secondary endpoint (PFS, Combo 450 vs. encorafenib) was not statistically significant; therefore, per protocol-specified testing hierarchy, the data in this PFS part 2 analysis are summarized descriptively without formal testing.

As pre-specified, (SAP version IV), the Part 2 initial CSR reports data from the combined Part 1 and Part 2 encorafenib monotherapy patients (N=280) and Part 2 encorafenib monotherapy patients only (N=86) through to the cut-off date for the Part 2 report.

All efficacy analyses were performed using the full analysis set (FAS).

Results

Part 2 patients were randomised between 19 March 2015 and 12 November 2015. A total of 344 patients were randomised during Part 2, 258 patients in the Combo 300 arm and 86 in the encorafenib arm.

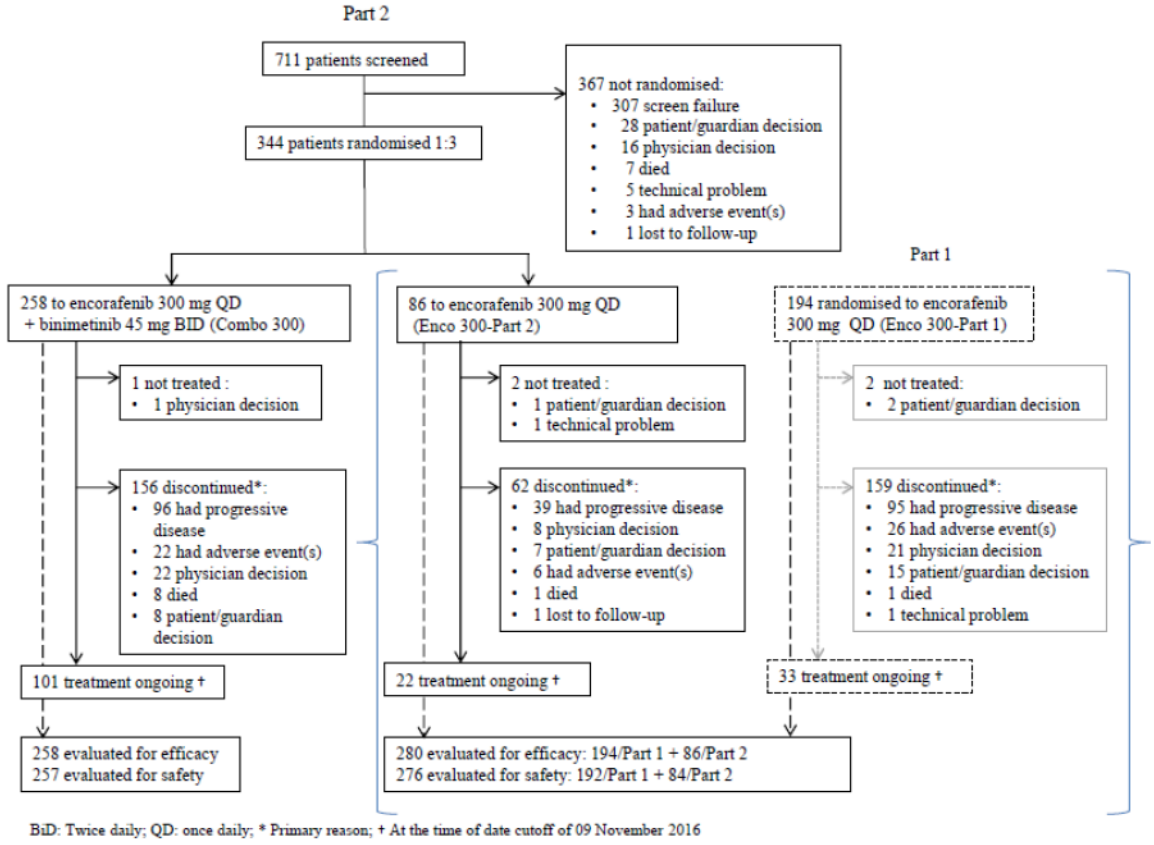


Figure 18: Patient flow chart for Part 2 of study CMEK162B2301

The two treatment groups (Combo 300 and Enco 300 [Parts 1 + 2]) were reasonably well balanced in terms of baseline and disease characteristics. As would be expected because these were directly randomised groups, the Combo 300 and Enco 300 Part 2 populations were similar at baseline.

However, there were some differences between the two encorafenib monotherapy arms (Part 1 and Part 2). Patients in the encorafenib Part 2 arm were older (median age 57 years, 30.2% were ≥ 65 years old) than those in the encorafenib Part 1 arm (median age 54 years, 20.6% were ≥ 65 years

old). The proportion of patients with Stage IV M1C with elevated LDH was higher in the Enco 300 Part 2 arm compared with Enco 300 Part 1 (37.2% vs. 25.8%). More Enco 300 Part 1 patients had Stage IV M1B (20.1% vs 11.6%), and Stage IV M1C with normal LDH (36.1% vs 30.2% respectively). A difference was seen in the overall duration of disease with a median time from initial diagnosis to randomisation that was nearly 5 months longer in the Enco 300 Part 2 population (28.4 vs 23.6 months). Distribution of disease location was similar between combinations for skin and/or lymph nodes; however more Enco 300 Part 1 patients had lung metastases (19.6% vs 8.1% respectively), while more patients in Enco 300 Part 2 had other organs involved. Baseline LDH levels were higher in Enco 300 Part 2 patients, with a mean of 338 U/L vs 265 UI/L and a median of 217 U/L vs 189 U/L vs respectively.

Table 52: Patient and Disease Characteristics (Full Analysis Set, Part 2 Initial)

Disease history	Combo 300 N=258	Encorafenib (Part 1 + Part 2) N=280	Encorafenib (Part 1) N=194	Encorafenib (Part 2) N=86
Primary site of cancer, n (%)				
Skin Melanoma	239 (92.6)	271 (96.8)	192 (99.0)	79 (91.9)
Unknown	19 (7.4)	9 (3.2)	2 (1.0)	7 (8.1)
Stage at time of study entry, n (%)				
Stage IIIB	0	2 (0.7)	2 (1.0)	0
Stage IIIC	8 (3.1)	9 (3.2)	4 (2.1)	5 (5.8)
Stage IV M1A	31 (12.0)	42 (15.0)	29 (14.9)	13 (15.1)
Stage IV M1B	47 (18.2)	49 (17.5)	39 (20.1)	10 (11.6)
Stage IV M1C	172 (66.7)	178 (63.6)	120 (61.9)	58 (67.4)
Stage IV M1C with elevated LDH [c]	73 (28.3)	82 (29.3)	50 (25.8)	32 (37.2)
Stage IV M1C with normal LDH	99 (38.4)	96 (34.3)	70 (36.1)	26 (30.2)
Time from initial diagnosis to onset of metastatic disease (months)				
n	249	276	191	85
Mean (SD)	28.13 (45.617)	36.53 (58.902)	36.45 (62.708)	36.72 (49.639)
Median	10.41	14.31	13.04	15.84
Min - Max	0 - 306.7	0 - 388.8	0 - 388.8	0 - 262.4
Number of organs involved at Baseline [a], n (%)				
1	78 (30.2)	79 (28.2)	56 (28.9)	23 (26.7)
2	66 (25.6)	74 (26.4)	52 (26.8)	22 (25.6)
3	59 (22.9)	61 (21.8)	42 (21.6)	19 (22.1)
>3	55 (21.3)	66 (23.6)	44 (22.7)	22 (25.6)
LDH at Baseline (U/L)				
n	258	280	194	86
Mean (SD)	300.8 (319.24)	287.7 (293.43)	265.2 (251.21)	338.4 (368.19)
Median	201.5	197.0	188.5	217.0
Min - Max	103 - 3095	75 – 2101	75 - 1886	115 - 2101
LDH at Baseline [b], n (%)				
Low	0	0	0	0
Normal	178 (69.0)	201 (71.8)	147 (75.8)	54 (62.8)
High [c]	80 (31.0)	79 (28.2)	47 (24.2)	32 (37.2)

Abbreviations: eCRF = electronic case report form; L = liter(s); LDH = lactate dehydrogenase; Max = maximum; Min = minimum; SD = standard deviation; U = units
Note: The time from initial diagnosis to onset of metastatic disease are calculated only for patients with metastatic disease. A patient may have multiple metastatic sites.
Note: Metastatic sites and organs involved were derived from Diagnosis and Extent of Cancer eCRF page.
[a] For patients with stage IIIB and IIIC at study entry, the number of organs involved at baseline is equal to one and presented as skin.
[b] Low and high categories defined by normal ranges.
[c] Some discrepancies were noted between the numbers of patients with Stage IV M1c LDH elevated and LDH high at baseline. The LDH level assessed for staging (M1c LDH elevated) was determined at screening whereas baseline values were used to report LDH at baseline. Also patients with Stage III disease could have elevated LDH.
Source: Table 14.1-3.2.1b; Table 14.1-3.3.1b

Combo 300 vs Enco 300 (Parts 1 and 2)

The median follow-up for PFS per BIRC (Kaplan-Meier) was 13.9 months for the Combo 300 arm and 18.5 months for the encorafenib (Parts 1 + 2) group.

For the primary analysis of Part 2 the PFS in the Combo 300 arm was 3.7 months longer than that of the encorafenib (Parts 1 + 2) group, with median PFS estimates of 12.9 months (95% CI 10.1, 14.0) and 9.2 months (95% CI 7.4, 11.0), respectively (HR=0.77, 95% CI 0.61, 0.97; nominal one-sided p=0.015).

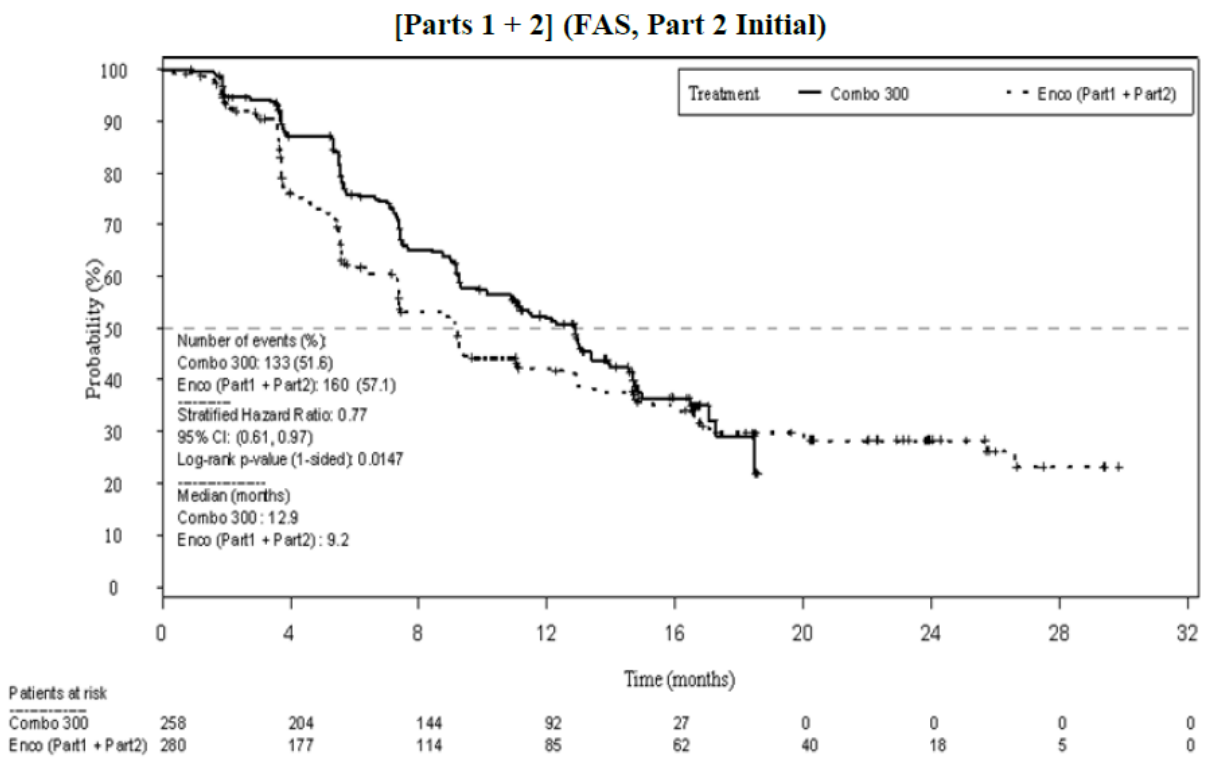


Figure 19: Kaplan-Meier Estimate of PFS Based on BIRC – Combo 300 vs. Enco 300 (Part 1 and 2)

The analysis was supported by the sensitivity analysis of the Investigator assessment (HR=0.72, 95% CI: 0.57, 0.91; nominal p=0.003), which had the same median PFS values as those by BIRC at 12.9 months (95% CI: 10.9, 14.8) and 9.2 months (95% CI: 7.4, 11.1) for the Combo 300 arm and the encorafenib (Parts 1 + 2) group.

Sensitivity analyses of PFS by BIRC were conducted: per protocol, unstratified, actual event, backdating and further anticancer therapy yielded similar HRs (0.75 – 0.78).

Most subgroup analyses of PFS per BIRC demonstrated point estimates in favour of the Combo 300 arm. In the 3 subgroups for which point estimates were in favour of the encorafenib (Parts 1 +2) group (*BRAF* V600K mutation status, AJCC stage IIIb-IVM1B and one organ involved at baseline), all had large 95% CIs which overlapped with the other subgroup of the respective category.

The confirmed ORR per BIRC in the Combo 300 arm was 65.9% (95% CI: 59.8, 71.7) compared with 50.4% (95% CI 44.3, 56.4) in the Enco 300 (Parts 1 + 2) group. Responses were of similar duration with a median DOR for confirmed responses per BIRC of one year in each treatment group (Combo 300 arm=12.7 months [95% CI: 9.3, 15.1]; encorafenib (Parts 1 + 2) group=12.9 months [95% CI 8.9, 15.5].

The ORR per Investigator review was higher in both the Combo 300 arm and the encorafenib (Parts 1 + 2) group than by BIRC, with the difference in favour of Combo 300 maintained (72.5% Combo 300 arm, 56.4% Enco 300 [Parts 1 + 2] group). Median DORs per Investigator were approximately 13 months in each treatment group.

Combo 300 vs. Enco 300 Part 2

PFS including only the encorafenib monotherapy patients who were concurrently randomised in Part 2 was conducted as a sensitivity analysis as per protocol. The median follow-up for PFS per BIRC

(Kaplan-Meier) was 13.9 months for the Combo 300 arm and 14.8 months for the encorafenib Part 2 arm.

In patients randomised concurrently in Part 2 of the study, there was an estimated 43% risk reduction in BIRC-assessed PFS in the Combo 300 arm (N=258) compared to the encorafenib monotherapy arm (N=86); HR=0.57, 95% CI: 0.41, 0.78; nominal stratified one-sided log-rank p<0.001. Median PFS was 12.9 months (95% CI: 10.1, 14.0) and 7.4 months (95% CI: 5.6, 9.2), respectively.

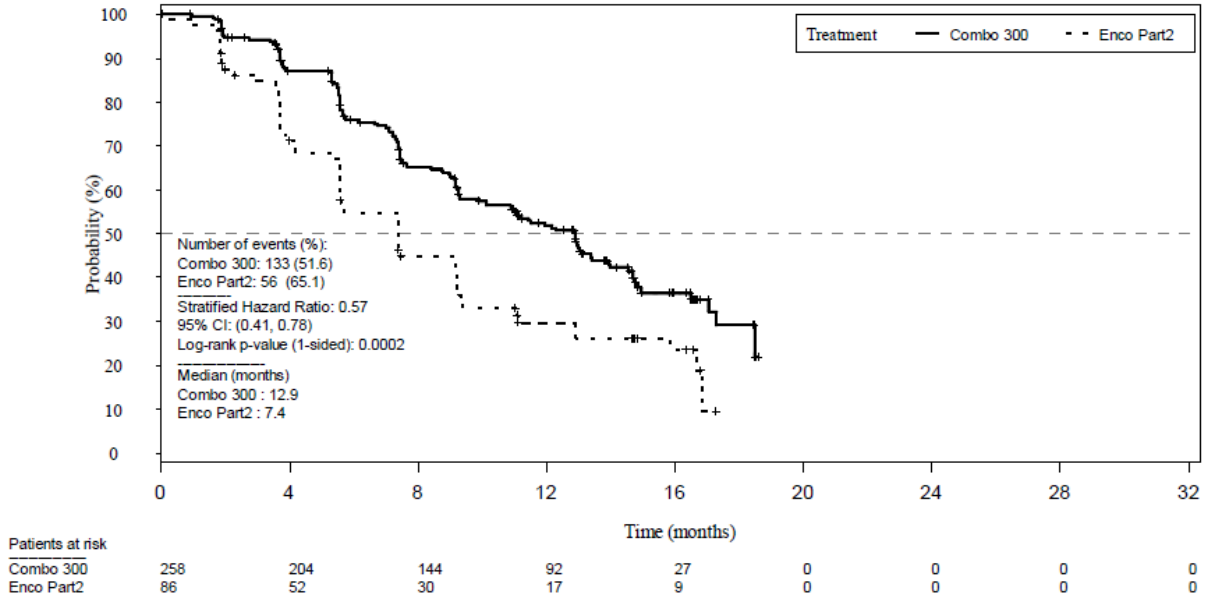


Figure 20: Kaplan-Meier Estimate of PFS Based on BIRC – Combo 300 vs. Enco 300 [Part 2] (FAS, Part 2 Initial)

The effect of treatment on PFS was estimated using a non-adjusted regression analysis, stratified by the study randomisation stratification factors (ECOG and disease stage). The crude HR was 0.57 (95% CI: 0.42, 0.79).

The four Propensity Score approaches including stratification (3 and 5 strata), matching, and IPW showed a benefit of Combo 300 over Enco 300 Part 2. HRs ranged from 0.52 to 0.70 (upper 95% cI 0.80 to 1.00).

PFS by BIRC – Encorafenib 300 Part 1 vs. Encorafenib 300 Part 2

Results of the prespecified sensitivity analysis of PFS by BIRC for the encorafenib arm (Part 1) vs. encorafenib arm (Part 2) showed an estimated 32% risk reduction in the encorafenib (Part 1) arm (HR 0.68; 95% CI: 0.49, 0.95; nominal one-sided p=0.013). The median PFS times of the encorafenib Part 1 arm vs. Part 2 arm were 9.6 months (95% CI: 7.4, 14.8) and 7.4 months (95% CI: 5.6, 9.2), respectively.

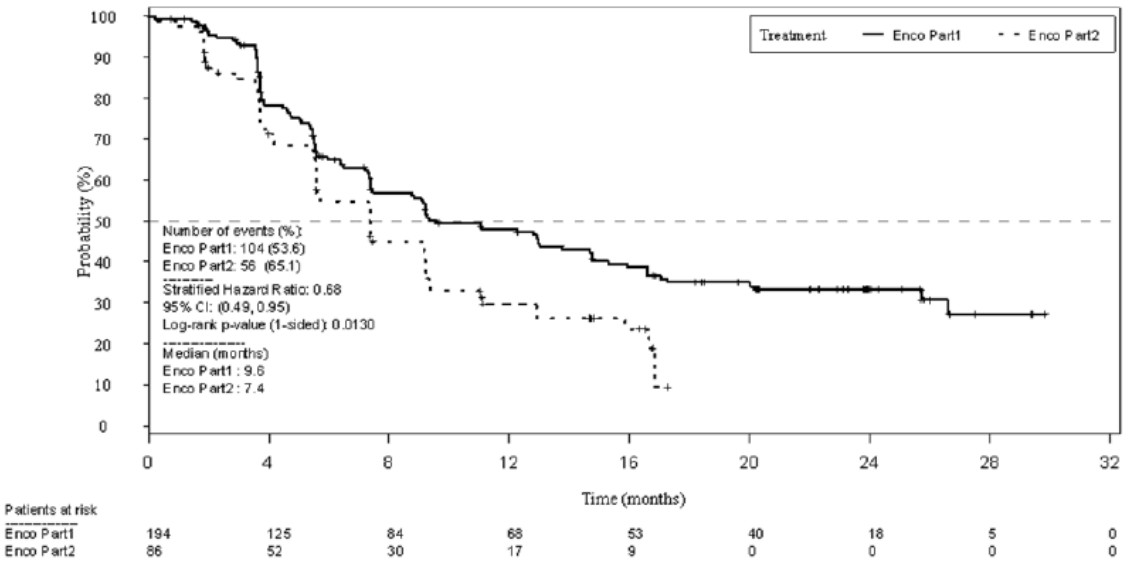


Figure 21: Kaplan-Meier plot of PFS by BIRC - Encorafenib Part 1 vs Encorafenib Part 2 (Full Analysis Set, Part 2 Initial)

PFS analyses of Enco 300 Part 1 vs Part 2, adjusted for confounding factors in the context of two independent cohorts, were conducted using the propensity score (PS) test. However, the PS is normally used for the description of populations accrued at a similar time point, whereas Enco 300 populations were recruited sequentially in Parts 1 and 2. The model cannot account for the potential bias introduced by this temporal difference.

Table 53: Comparison of Baseline Covariates for Enco Part 1 vs. Enco Part 2

	P-value
Sex	0.4849[1]
Age	0.2453
Baseline Body Mass Index (kg/m)	0.0110
Race	0.7956[1]
Region	0.0034[1]
ECOG at baseline first dose	0.9901[1]
Time from initial diagnosis to first metastasis	0.4192
Primary site of cancer at study entry	0.0043[2]
Stage	0.3792[1]
BRAF status	0.4316[1]
Number of organs involved at baseline	0.8712[1]
Baseline brain metastases	0.7287[2]
Baseline liver metastases	0.0892[1]
Prior adjuvant immunotherapy	0.1372[1]
LDH at baseline (U/L)	0.0177

Tests: Wilcoxon for continuous variables, Chi-square (1) or Fisher (2) for categorical variables.

The effect of treatment on PFS was estimated using a non-adjusted regression analysis, stratified by the stratification factors (ECOG performance status and stage). The crude HR was 0.69 (95% CI: 0.49, 0.96).

Four PS approaches including stratification (3 and 5 strata), matching, and IPW were then used to estimate the treatment effect on PFS and were adjusted for confounding. The different PS methods

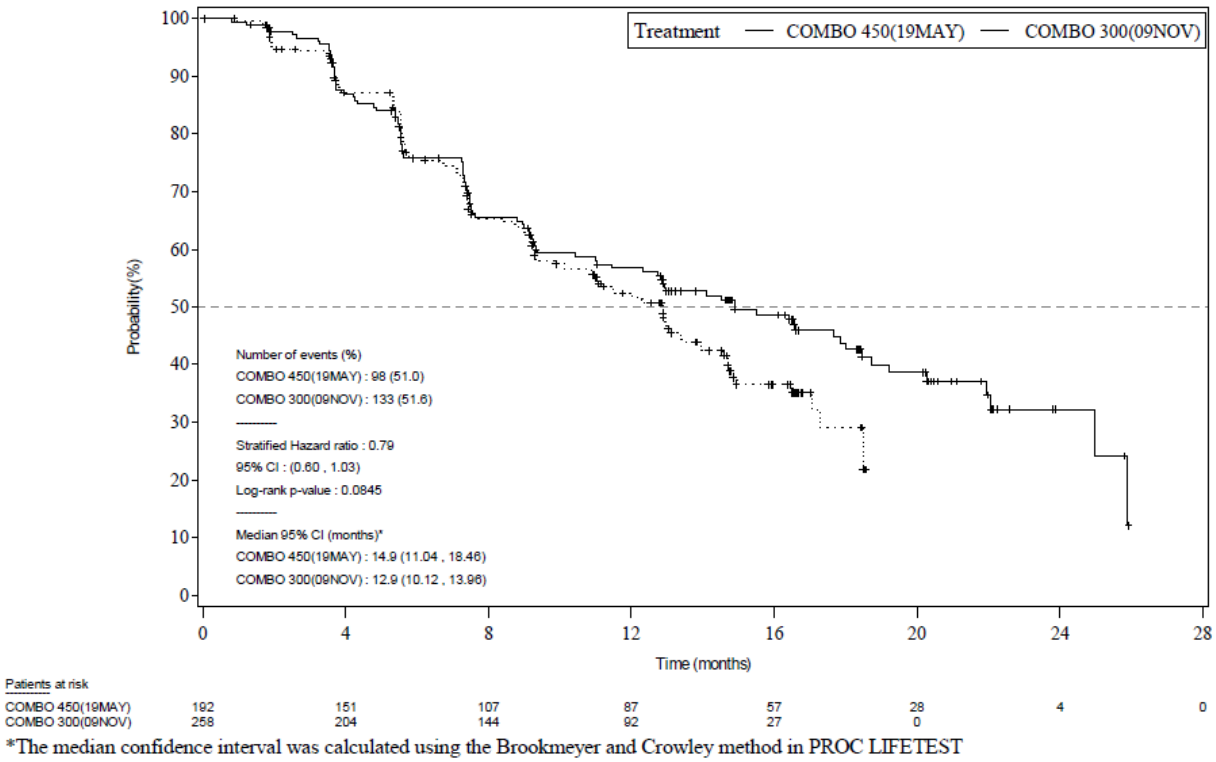
(adjusted and non-adjusted) gave HRs ranging from 0.57 to 0.68 and all showed a significant increase in the risk of disease progression or death for Enco 300 in Part 2 over Enco 300 in Part 1.

Contribution of binimetinib 45 mg BID to the efficacy of Combo 450: Combo 450 vs. Combo 300

A post hoc comparison of data from the Combo 450 arm [Part 1 of CMEK162B2301 (N=192) at the cut-off date for the primary analysis of 19 May 2016] and the Combo 300 arm [Part 2 (N=258) unplanned initial analysis at the cut-off date of 09 November 2016] was conducted. The two data cut-offs were chosen to allow similar duration of follow up, as the populations were not recruited concomitantly. Median potential follow-up for PFS was comparable for the two populations (16.7 months vs 13.9 months) and the median follow-up time was 9.3 months for both combinations. A supportive analysis was performed using the 09 November 2016 for the two arms.

The Combo 450 and Combo 300 populations were similar in terms of age, sex, race and ECOG performance status. A slightly higher proportion of patients was enrolled in Europe, North America and Australia in Combo 450 compared to Combo 300 (9.5% difference). Median time from initial diagnosis to onset of metastatic disease was longer in the Combo 450 than the Combo 300 population (15.0 vs 10.4 months). Distribution of disease location and disease burden were similar between combinations, although a higher proportion of patients had only one disease site in Combo 300 (30.2% vs 24.5% with Combo 450). Median LDH levels at baseline were slightly higher in Combo 300 (202 vs. 173 U/L).

Median PFS (per BIRC) was 2 months longer for Combo 450 (14.9 months) than for Combo 300 (12.9 months), but the difference was not statistically significant (log rank p value 0.0845).



*The median confidence interval was calculated using the Brookmeyer and Crowley method in PROC LIFETEST

Figure 22: Kaplan-Meier PFS Comparison for Combo 450 (cut-off date: 19 May 2016) vs Combo 300 (Cut-off date: 09 November 2016) - FAS Population

Table 54: Direct Comparison of Combo 450 (cut-off date: 19 May 2016) vs Combo 300 (Cut-off date: 09 November 2016) - FAS Population - Stratified Analyses

	Combo 450 Part 1 (N=192)	Combo 300 Part2 (N=258)
PFS by BIRC		
# events n/N (%)	98/192 (51.0%)	133/258 (51.6%)
Median (95% CI) in months	14.9 (11.0, 18.5)	12.9 (10.1, 14.0)
Log-rank p-value (*)	0.0845	
Generalized Wilcoxon p-value (*)	0.3647	
HR (95% CI) (*)	0.79 (0.60, 1.03)	
PFS by Investigator		
# events n/N (%)	102/192 (53.1%)	136/258 (52.7%)
Median (95% CI) in months	14.8 (10.4, 18.4)	12.9 (10.9, 14.8)
Log-rank p-value (*)	0.1918	
Generalized Wilcoxon p-value (*)	0.4569	
HR (95% CI) (*)	0.84 (0.64, 1.09)	
Confirmed Response per BIRC		
# responders (%)	121 (63.0%)	170 (65.9%)
95% CI	(55.8, 69.9)	(59.8, 71.7)
Confirmed DCR per BIRC		
# responders (%)	177 (92.2%)	234 (90.7%)
95% CI	(87.4, 95.6)	(86.5, 93.9)
Duration of Confirmed Response per BIRC		
# responders n/N (%)	54/121 (44.6%)	81/170 (47.6%)
Median (95% CI)	16.6 (12.2, 20.4)	12.7 (9.3, 15.1)

Other efficacy parameters by BIRC showed similar results for the two combinations (ORR = 63.0% vs 65.9% and DCR = 92.2% vs 90.7%, respectively). However, the duration of confirmed responses was longer for Combo 450 vs Combo 300 (16.6 months vs 12.7 months) which is aligned with the difference in PFS.

Similar results were seen when comparing median PFS per Investigator (14.8 vs 12.9 months, respectively). ORRs per Investigator review were also similar, although higher (75.0% vs 72.5%).

The analysis performed using the 09 November 2016 cut-off date for the two arms was supportive.

Table 55: Direct Comparisons Combo 450 vs Combo 300 (Cut-off date for both: 09 Nov 2016) - FAS Population - Stratified Analyses

	Combo 450 P1 (N=192) 09Nov2016	Combo 300 P2 (N=258) 09Nov2016
PFS by BIRC		
# events n/N (%)	104/192 (54.2%)	133/258 (51.6%)
Median (95% CI) in months	15.5 (11.0, 20.2)	12.9 (10.1, 14.0)
Event-free at 12 months, % (95% CI)	56.7 (48.8, 63.9)	51.9 (45.1, 58.2)
Log-rank p-value (*)	0.0573	
Generalized Wilcoxon p-value (*)	0.3205	
HR (95% CI) (*)	0.77 (0.58, 1.01)	
PFS by Investigator		
# events n/N (%)	109/192 (56.8%)	136/258 (52.7%)
Median (95% CI) in months	14.8 (10.4, 18.4)	12.9 (10.9, 14.8)
Event-free at 12 months, % (95% CI)	53.8 (46.0, 60.9)	50.5 (43.9, 56.8)
Log-rank p-value (*)	0.1664	
Generalized Wilcoxon p-value (*)	0.4314	
HR (95% CI) (*)	0.83 (0.63, 1.08)	

(*) two-sided p-values. Log-rank test, Wilcoxon's test and Cox PH model are stratified by IVRS AJCC and ECOG performance status

The multivariate Cox regression model stratified by the study stratification factors the applicant concluded a benefit of Combo 450 over Combo 300 for PFS when adjusting for the main prognostic factors [HR 0.74 (95% CI 0.56-0.98), nominal p value =0.0387] at the cut-off dates for initial analysis (19 May 2016 and 9 November 2016, respectively).

The propensity score was estimated using a logistic regression model that incorporates 14 variables potentially related to the outcome and/ or treatment decision.

Table 56: Comparison of Baseline Covariates for Combo 450 and Combo 300

	P-value
Sex	0.7702[1]
Age	0.5053
Baseline BMI (kg/m)	0.2979
Race	0.2601[1]
Region	0.0067[1]
ECOG at baseline [a]	0.5704[1]
Time from initial diagnosis to first metastasis	0.0453
Stage	0.5653[1]
BRAF status	0.5846[1]
Number of organs involved at baseline	0.3332[1]
Baseline brain metastases	0.2633[1]
Baseline liver metastases	0.8398[1]
Prior adjuvant immunotherapy	0.0970[1]
LDH at baseline (U/L)	0.0128

[a] Last non-missing ECOG performance status prior to or on the start of study treatment for patients who took at least one study treatment or prior to or on Cycle 1 Day 1 for patients who didn't take any study treatment.

Tests: Wilcoxon for continuous variables, Chi-square (1) or Fisher (2) for categorical variables.

The effect of treatment on PFS was estimated using a non-adjusted regression analysis, stratified by the study stratification factors (ECOG and Stage). Then four PS approaches, including stratification (3

and 5 strata), matching, and inverse probability weighting (IPW), were used to estimate the treatment effect on PFS and adjust for confounding factors. The different PS methods (adjusted and non-adjusted) gave similar results when comparing Combo 450 and Combo 300 for PFS, reaching an HR of 0.75 to 0.79, with an upper 95% CI above 1 (1.01 to 1.09).

Ancillary analyses

None.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table EF-03: Summary of efficacy for trial CMEK162B2301 (COLUMBUS, Part 1 only)

Title: A 2-part phase III randomized, open label, multicentre study of LGX818 plus MEK162 versus vemurafenib and LGX818 monotherapy in patients with unresectable or metastatic BRAF V600 mutant melanoma			
Study identifier	B2301		
Design	2-part, multicentre, randomised, 3-arm, open-label		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Until PD/ unacceptable toxicity/ death Screening up to 21 days Follow-up post study drug discontinuation
Hypothesis	Superiority		
Treatments groups	Combo 450		Encorafenib 450mg QD + binimetinib 45mg BID, N= 192
	Enco 300		Encorafenib 300mg QD, N= 194
	Vemurafenib		Vemurafenib 960mg BID, N=191
Endpoints and definitions	Primary endpoint	PFS by BIRC	Combo 450 vs. vemurafenib
	Key secondary endpoint	PFS by BIRC	Combo 450 vs. encorafenib
	Other secondary endpoints	ORR	Assess ORR by treatment arms
Database lock	19 May 2016		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (Full analysis set) read centrally by a BIRC			
Descriptive statistics and estimate	Treatment group	Combo 450	Enco 300	Vemurafenib

variability	Number of subjects	192	194	191
	Median PFS per BIRC (months)	14.9	9.6	7.3
	95% CI	11.0, 18.5	7.5, 14.8	5.6, 8.2
	ORR per BIRC (%)	63.0	50.5	40.3
	95% CI	55.8, 69.9	43.3, 57.8	33.3, 47.6

Effect estimate per comparison	Primary endpoint	Comparison groups	PFS Combo 450 vs. Vemurafenib
		HR	0.54
		95% CI	0.41, 0.71
		1 sided stratified log rank P-value	<0.001
	Key secondary endpoint	Comparison groups	PFS Combo 450 vs Enco 300
		HR	0.75
		95% CI	0.56, 1.00
		1 sided P-value	0.026

Analysis performed across trials (pooled analyses and meta-analysis)

The applicant did not submit analyses across trials.

Clinical studies in special populations

In study B2301 the following proportions of patients aged ≥65 years were recruited to each treatment arm.

Table 57: Proportions of patients aged ⩾65 years were recruited to each treatment arm

	Encorafenib 450mg + Binimetinib N=192	Encorafenib N=194	Vemurafenib N=191	Total N=577
Age ≥65 years, n(%)	60 (31.3)	40 (20.6)	51 (26.7)	151 (26.2)

Table 58: Unstratified Cox Regression Model for PFS per Central Review by Subgroup – age ⩾ 65 years (FAS, Part 1)

	Event N (%)	Median Time [2] months (95% CI)	Cox model [1]	
			Hazard ratio	95% CI
Age ≥ 65 years				
Combo 450	29/ 60 (48.3)	11.0 (7.6, NE)		
Encorafenib [3]	21/ 40 (52.5)	8.0 (5.4, 15.9)	0.71	(0.40, 1.25)
Vemurafenib [4]	26/51 (51.0)	7.3 (4,1. 11.0)	0.66	(0.39, 1.12)

[1] Cox PH model are unstratified.
[2] Median (time to event) and its 95% CI are generated by KM estimation.

[3] Analyses comparing Encorafenib 450 + Binimetinib versus Encorafenib (Part 1) only consider data from patients randomized to those treatment groups. Hazard ratio Encorafenib 450mg + Binimetinib versus Encorafenib. Encorafenib is the reference group.
[4] Analyses comparing Encorafenib 450 + Binimetinib versus Vemurafenib only consider data from patients randomized to those treatment groups. Hazard ratio Encorafenib 450mg + Binimetinib versus Vemurafenib. Vemurafenib is the reference group.

Supportive study(ies)

Supportive study: CLGX818X2109- LOGIC 2

Study **CLGX818X2109** (LOGIC 2) is an ongoing multicentre, open-label, 2-part Phase 2 study of sequential LGX818/MEK162 (encorafenib/binimetinib) combination followed by a rational combination with targeted agents after progression, with the aim of overcoming resistance in adult patients with locally advanced or metastatic BRAF V600 melanoma. There was no control group.

BRAF mutation was assessed from blood samples locally and from tumour samples (archival or fresh), both locally and centrally. Eligibility was based on local tumour *BRAF* mutation results and included all V600 mutations (e.g. V600E, K, D, L or R).

Patients were to be ≥ 18 years of age with AJCC stage IIIC or IV melanoma, measurable disease as determined by RECIST v1.1 and an ECOG PS of ≤2. Patients were to have no symptomatic brain metastases or symptomatic/ untreated leptomeningeal disease. No prior treatment was allowed with radiation therapy (> 30% of the bone marrow reserve), chemotherapy, biological therapy within ≤ 4 weeks or small molecule therapeutics or investigational agents within 5-half-lives prior to starting study drug. Patients had to have recovered from the side effects of prior therapy.

In Part 1, patients were treated with the recommended Phase 2 dose (RP2D) of encorafenib 450mg QD in combination with binimetinib 45 mg BID [Combo 450]) until PD (as defined per RECIST v1.1) or no clinical benefit. Three different patient populations were included:

• Group A: Patients naïve to treatment with BRAF inhibitors

• Group B: Patients who progressed after single-agent BRAF or MEK inhibitor or after combination BRAF and MEK inhibitors other than binimetinib/encorafenib or receiving binimetinib and/or encorafenib, who had not progressed yet or, in consultation with the Sponsor, who received any BRAF and/or MEK inhibitor other than binimetinib and/or encorafenib and had not progressed yet.

• Group C: Patients who progressed after binimetinib/encorafenib combination therapy

In Part 2, patients previously treated with binimetinib/encorafenib combination therapy and who relapsed on this therapy received tailored combination treatment with binimetinib/encorafenib and a third agent in one of four arms based on genetic assessment of a tumour biopsy obtained at disease progression. The four agents were BKM120 (PI3K inhibitor), BGJ398 (FGFR inhibitor), INC280 (cMET inhibitor) and LEE011 (CDK 4/6 inhibitor).

No primary efficacy endpoint was defined for Part 1 as it was designed as a run-in stage for Part 2 to allow patients initially naïve to treatment with BRAF/MEK inhibitors (Group A) to meet the Part 2 eligibility criterion of being resistant to the MEK/BRAF inhibitor combination.

The primary efficacy endpoint for Part 2 of the study was the ORR, defined as the proportion of patients with a best overall response [BOR] of CR or PR as determined by the Investigator using RECIST v1.1. The key secondary endpoint was PFS with other secondary endpoints of DOR, TTR (time to response), DCR (disease control rate) and OS. Evaluations of ORR, PFS, DOR, TTR and DCR were

also performed and analysed for Part 1. The CSR for Part 1 presents data for Groups A, B and C but the focus here is on data from Group A i.e. BRAF and MEK inhibitor-naïve patients. The FAS included all patients who received at least one dose of encorafenib or binimetinib and was used for the analysis of all endpoints unless noted otherwise.

A total of 75 treatment-naïve patients were enrolled into Part 1 (Group A) of the study between 31 July 2014 and 15 January 2016. As of the data cut-off (18 February 2016), 44 patients (58.7%) were ongoing with Combo 450 treatment. The most common reason for discontinuation from Combo 450 study treatment was PD (25.3%). As of the data cut-off, 13 patients (17.3%) had continued to Part 2 of the study.

Table 59: Study CLGX818X2109: Patient Disposition (Treatment-Naïve Patients, Part 1)

Disposition Reason	Combo 450 (Treatment-Naïve) N =75 n (%)
Patients treated in Part 1	
Treatment ongoing [a]	44 (58.7)
End of treatment	31 (41.3)
Primary reason for end of Part 1 treatment	
Adverse event(s)	3 (4.0)
Completed	0
Death	5 (6.7)
Physician decision	1 (1.3)
Progressive disease	19 (25.3)
Withdrawal by parent/guardian	3 (4.0)
Study follow-up after end of Part 1 treatment [b]	
Patients entering Part 2	13 (17.3)
Patients continuing to be followed for study evaluation [b]	2 (2.7)
Patients no longer being followed for study evaluation	16 (23.1)

[a] Patients ongoing at the time of the cut-off 18 February 2016.
[b] Patients in Part 1 who have ended treatment. This summary requires evaluation of data from Part 2 of the study which may be incomplete as the study is ongoing.

Most patients were Caucasian (n=74, 98.7%), and there were more males enrolled (n= 47, 62.7%) than females. The median age was 56 years and nearly a quarter were aged ≥65 years (n=18, 24%). Most patients had an ECOG PS of 0 (n=55, 73.3%) and had AJCC stage IV disease (93.3%) at study entry. Baseline LDH was high in 18.7% (n=14) of patients; however, 40 patients (53.3%) did not have a baseline LDH value reported as this was not required until Protocol Amendment 2 (November 2014).

The proportion of patients with skin melanoma as the primary site of cancer was lower than in Columbus (82.7% vs >99%) but, conversely, the proportion of patients with an unknown primary site was higher (6.7%). The most common sites of metastases were lymph nodes (70.7%), lung (57.3%), liver (40.0%) and bone (26.7%). Brain metastases at baseline were reported in 5.3% of patients. Forty-percent of patients had received prior-antineoplastic medication. More patients had received prior immunotherapy with ipilimumab (21%) than in study B2301 (≤5%). Patients could have had prior systemic chemotherapy and 2.7% of treatment-naïve patients in Study CLGX818X2109 had prior treatment with alkylating agents (dacarbazine, dacarbazine citrate).

Table 60: Study CLGX818X2109: Prior Cancer Therapy (Treatment-Naïve Patients, Part 1)

Disease history	Combo 450 (Treatment-Naïve) N =75 n (%)
Any therapy	

Medication	30 (40.0)
Surgery	74 (98.7)
Radiotherapy	18 (24.0)
Antineoplastic medication	
Protein kinase inhibitors	0
Monoclonal antibodies	21 (28.0)
Ipilimumab	16 (21.3)
Pembrolizumab	3 (4.0)
Nivolumab	5 (6.7)
Other	1 (1.3)
Interferons	12 (16.0)
Radiotherapy: setting at last radiotherapy	
Adjuvant	12 (16.0)
Therapeutic	1 (1.3)
Palliative	5 (6.7)

Protocol deviations in BRAF/MEK-treatment naïve patients were reported for 28.0% of patients, 4.0% were due to eligibility violations and 21.3% were assessment deviations.

At data cut-off (18 February 2016), the median duration of exposure to study treatment for treatment naïve patients was 31.14 weeks (range, 3.86 to 80.57). The confirmed ORR per investigator was 69.3% (95% CI 57.9, 79.5). Most patients experienced disease improvement or control, as the DCR was 90.7% (95% CI 81.7, 96.2).

Updated results from the data cut-off point of 30 December 2016 have been provided and are summarised in the table below.

Table 61: Study CLGX818X2109: Best Overall Response per Investigator Assessment (FAS, Part 1)

	Combo 450 (Treatment-Naïve) N =75 n (%)
Confirmed BOR[a, b]	
CR	6 (8.0)
PR	49 (65.3)
SD	15 (20.0)
PD	3 (4.0)
Unknown[c]	2 (2.7)
Confirmed ORR: CR + PR	55 (73.3)
95% CI[d]	(61.9, 82.9)
Confirmed DCR: CR+PR+ SD	70 (93.3)
95% CI[d]	(85.1, 97.8)

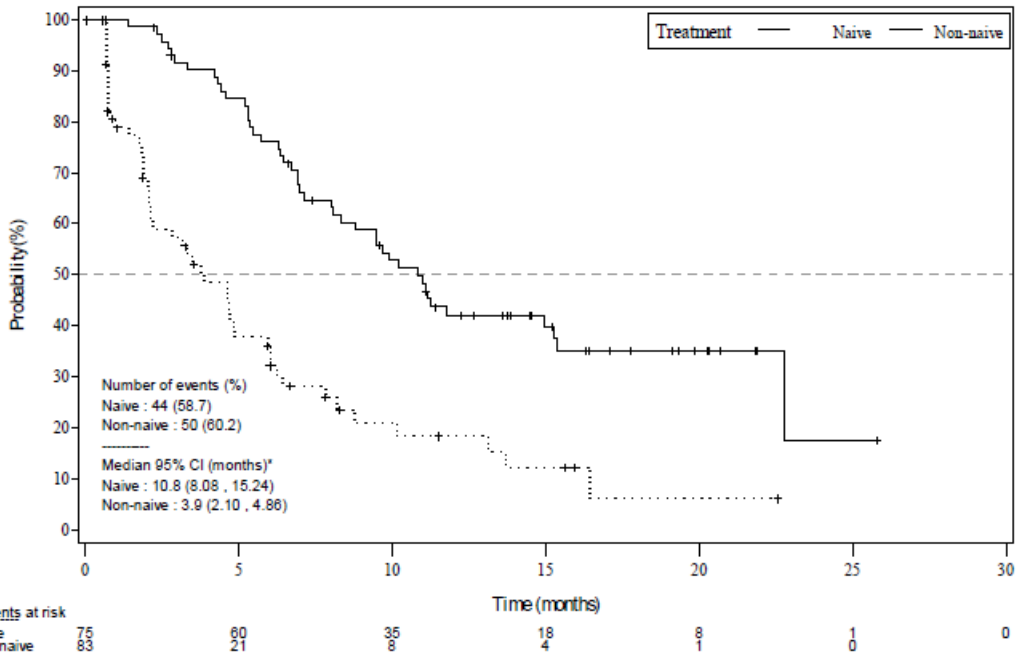
Source: Efficacy Appendix Table Q40BT 3.1
BID: twice daily; BOR: best overall response; Combo 450: binimetinib 45 mg BID in combination with encorafenib 450 mg QD; CR: complete response; DCR: disease control rate; ORR: objective response rate; PD: progressive disease; PR: partial response; QD: once daily; SD: stable disease
[a] Best overall response is based on local assessment using RECIST v1.1.
[b] CR and PR are confirmed by repeat assessments performed not less than 4 weeks after the criteria for response is first met.
[c] Unknown = Progression has not been documented and one or more lesions have not been assessed or have been assessed using a different method than baseline.
[d] The 95% CI for the frequency distribution of each variable were computed using Clopper-Pearson's method.

Table 62: Study CLGX818X2109: Kaplan-Meier Summary of PFS by Investigator Assessment (FAS, Part 1)

	Combo 450 (Treatment-Naïve) N =75 n (%)
Number of PFS events	44/75 (58.7)
Progression	38 (50.7)
Death without progression	6 (8.0)
Number censored	31 (41.3)
Percentiles (95% CI)[a] (months)	
25th	6.3 (4.6, 7.1)
50th	10.8 (8.1, 15.2)
75th	22.8 (15.4, NE)
Kaplan-Meier estimates (95% CI)[b]	
6 months	76.2 (64.5, 84.4)
12 months	42.1 (30.3, 53.5)
18 months	35.2 (23.4, 47.2)
24 months	17.6 (1.9, 46.6)

Source: Efficacy Appendix Table Q40BT1.1 and Q40B T1.2
[a] Represents the estimated time (95% CI), reported in months, at which the specified percentiles occur based on the Kaplan-Meier analysis. Note that the 50th percentile is the same as the median time to event. Values were calculated using the Brookmeyer and Crowley method in PROC LIFETEST. [b] Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point.

Table 63: Study CLGX818X2109: Kaplan-Meier Plot of PFS by Investigator Assessment (FAS, Part 1)



Source : Efficacy Appendix Figure Q40 B F.1, cut-off date: 30DEC2016
*The median confidence interval was calculated using the Brookmeyer and Crowley method in PROC LIFETEST.

2.5.1. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal study **CMEK162B2301 (COLUMBUS)** was a Phase 3, randomised, open label study comprising 2 parts. The primary endpoint was PFS with Combo 450 vs. vemurafenib. The key secondary endpoint was PFS with Combo 450 vs. Enco 300 from Part 1 (plus PFS Combo 300 vs. Enco 300 from Part 2). With the hierarchical testing procedure, the secondary endpoint of OS Combo 450 vs. vemurafenib was to be tested only if these comparisons were statistically significant. The PFS analyses were conducted after more than the planned number of events had occurred [204 PFS events (planned 145) for Combo 450 vs. vemurafenib and 223 PFS events (planned 191) for Combo 450 vs. Enco 300].

The DMC reviewed the results (and unblinded survival data) to which the applicant remained blinded and recommended that the planned analyses be terminated and all patients be informed of the Part 1 results. Patients in the vemurafenib arm were to be advised that a BRAF-MEK inhibitor combination might be a better alternative. There were no specific recommendations regarding the encorafenib monotherapy arm. The OS analysis will likely be confounded by patients in the monotherapy arms seeking alternative treatments. This early termination is probably inevitable as Combo 450 was being compared to single agent BRAF inhibitor which would not now be considered standard of care in this setting. Patients with V600 mutant tumours would routinely be treated with a BRAF-MEK inhibitor combination. Still, it is accepted that at the time the trial was designed, the combination of BRAF/MEK inhibitor was not the SoC..

The study was open label, given the likelihood of functional unblinding from the predicted treatment toxicities. Efficacy assessment by blinded independent review was appropriate to prevent evaluation bias. Progression free survival as the primary endpoint is accepted as a meaningful reduction in the risk of progression or death represents a clinical benefit in patients with *BRAF* mutation-positive melanoma. It also allowed for more rapid assessment, mitigating the potentially confounding effects of post-study treatments on OS. Overall, the design of the study is acceptable and the study was well conducted.

Supportive data is provided from Study **CLGX818X2109 (LOGIC 2)**, an open-label, single arm, Phase 2 trial. Data has been provided from a subsection of patients (n=75) in Part 1 – Group A – no prior treatment with a BRAF inhibitor. There was no pre-defined efficacy endpoint but ORR, PFS, DOR, TTR and DCR were evaluated and provided supportive evidence of efficacy.

Efficacy data and additional analyses

The primary endpoint of the pivotal study, CMEK162B2301, was met as Combo 450 significantly improved median PFS versus vemurafenib alone (14.9 vs. 7.3 months) based on BIRC review in the full analysis set (FAS) with a HR of 0.54 (95% CI, 0.41, 0.71) (one-sided stratified log rank $p<0.001$) which was statistically significant. PFS curves separate early (after approximately 1-2 months) and do not intersect until near the end of follow-up where the number of patients in each arm is ≤ 4. Median follow-up time for PFS per BIRC was 16.7 months for the Combo 450 arm and 14.4 months for the vemurafenib arm. About 50% of patients were censored at the time of the analysis, approximately 30% in the Combo 450 arm due to remaining on treatment and 20% in the vemurafenib arm for starting a new anti-cancer therapy. As the DMC recommended termination of further analyses and all patients in the vemurafenib arm receive BRAF-MEK inhibitor combination therapy there will be no further information on this direct comparison.

The sensitivity PFS analyses yielded similar HRs (95% CI) and median PFS values to the primary analysis, reflecting the robustness of the PFS benefit. These included the investigator assessment in the FAS, the per protocol set (PPS) and tumour assessments after initiation of further anti-cancer therapy. The efficacy results based on investigator assessment were consistent with the independent central assessment.

Other than treatment, the only prognostic factor that significantly influenced PFS was LDH increase of 125 IU/L. The PFS benefit was consistent across the subgroups analysed, apart from the presence of brain metastases. Only 12 patients (9 Combo 450 and 3 vemurafenib) had brain metastases at baseline so there were insufficient patients to evaluate efficacy in this subgroup. All patients had BRAF mutant V600 E or K melanoma, which comprise most BRAF mutant patients Across the 3 treatment arms only 24 patients (3.7% of the Combo 450 arm) had received prior ipilimumab in the adjuvant or metastatic setting and 3 patients (0.5% of the Combo arm) had received a prior anti PD1/PDL1 inhibitor in the metastatic setting. The HR favoured Combo 450 in the small group of patients that had received prior immunotherapy (n=15; 8 Combo 450 vs 7 vemurafenib) although the confidence intervals were large. The use of Combo 450 in patients previously treated with a BRAF or MEK inhibitor is not supported. The median PFS in non-naïve patients in LOGIC 2 was 3.5 months.

Results for overall survival have been presented from the OS interim analysis with cut-off date 7th November 2017, by which time a total of 232 OS events were observed in the Combo 450 and vemurafenib arms combined in Part 1 of the study. The median OS was 33.6 months (24.4, 39.2) and 16.9 months (14.0, 24.5), respectively, for patients treated with Combo 450 compared to those treated with vemurafenib with a HR 0.61 (95% CI 0.47, 0.79, nominal p value <0.0001). The median OS was 33.6 months (24.4, 39.2) and 23.5 months (19.6, 33.6), respectively, for patients treated with Combo 450 compared to those treated with encorafenib with a HR 0.81 (95% CI 0.61, 1.06, nominal p value=0.0613). The observed HR and numerical increase in median OS supports the relevant contribution of binimetinib and demonstrates a statistically significant and clinically meaningful improvement in overall survival with the combination treatment of binimetinib and encorafenib compared with vemurafenib.

For Combo 450 vs vemurafenib and Combo450 vs encorafenib, results of the planned sensitivity analyses were consistent with those from the interim OS analysis and lead to similar conclusions about treatment effect. Most unstratified subgroup analyses also demonstrated median OS point estimates in favour of the Combo 450.

For the key secondary efficacy endpoint, the median PFS estimates by BIRC in the FAS were 14.9 and 9.6 months for Combo 450 and encorafenib, respectively, with a HR of 0.75 (95% CI 0.56, 1.00). The PFS difference of 5.3 months just missed statistical significance (p = 0.0256) by the one-sided stratified log-rank test with a threshold of p < 0.025. Therefore, by the hierarchical testing procedure none of the further endpoints can be considered statistically significant and nominal p values are presented for descriptive purposed only. Per Investigator assessment of response, the PFS difference between the Combo 450 and the encorafenib arm was consistent with that reported by the BIRC (14.8 months Combo 450 vs. 9.2 months Enco 300) and this difference reached nominal significance at the one-sided 0.025 level (HR 0.68; 95% CI 0.52, 0.90; nominal 1-sided p=0.003). The subgroup analyses, including the unstratified HRs, were generally consistent with the analysis in the full population, allowing for wide confidence intervals in the subgroups with small numbers of patients. There were some groups with small patient numbers where the HR was greater than 1 (e.g. number of organs involved at baseline 1 or >3) but this is likely due to chance. Unstratified subgroup analyses demonstrated point estimates in favour of Combo 450, including LDH at baseline, ECOG performance status and AJCC stage. This supports benefit for the combination over single agent encorafenib, likely

due to the increased tolerability of encorafenib with a MEK inhibitor allowing a higher dose of encorafenib to be administered (450mg vs 300mg) as well as the anti-tumour contribution of binimetinib itself.

Part 2 of Study CMEK162B2301 was designed to assess the contribution of binimetinib to the encorafenib and binimetinib combination. Preliminary Part 2 data, at a cut-off date of 9 November 2016, demonstrated the contribution of binimetinib with an improved median PFS estimate of 12.9 months (95% CI: 10.1, 14.0) for Combo 300 compared to 9.2 months (95% CI: 7.4, 11.0) for Enco 300 (Parts 1 and 2) per independent central review (BIRC). The confirmed ORR per BIRC was 65.9% (95% CI: 59.8, 71.7) for Combo 300 and 50.4% (95% CI: 44.3, 56.4) for Enco 300 (Parts 1 and 2). Median DOR for confirmed responses per BIRC was 12.7 months [95% CI: 9.3, 15.1] for Combo 300 and 12.9 months [95% CI: 8.9, 15.5] for Enco 300. The median duration of treatment was longer for Combo 300 vs Enco 300, 52.1 weeks vs 31.5 weeks. The addition of binimetinib 45mg BID to encorafenib 300mg QD increased the median PFS by 3.7 months (stratified HR 0.77, 95% CI 0.61, 0.97; nominal 1-sided p=0.015) and the ORR by 15.5%. The investigator assessment and sensitivity analyses of PFS were similar. When only the patients randomised to Part 2 were assessed the results again supported a binimetinib contribution to efficacy; median PFS values (95% CI) were 12.9 months (10.1, 14.0) and 7.4 months (5.6, 9.2), respectively (HR 0.57, 95% CI: 0.41, 0.78; nominal one-sided p<0.001 per stratified log-rank test). However, it is worth noting that the results for encorafenib monotherapy are better in part 1 than part 2 with a difference of over 2 months in median PFS. It is possible that differences in baseline characteristics (in particular age, stage of disease and elevated LDH) may be responsible for this difference in outcome. Some baseline imbalances can also be seen between Combo300 and Enco300 part 2. In particular, a greater proportion of the Enco 300 patients (Part 2) have Stage IV disease with elevated LDH compared with the Combo 300 patients.

Therefore, for patients that must reduce the dose to 300 mg due to ADRs, the data seems to indicate that patients will continue to have a similar magnitude of treatment effect. The proposed dose regimen in the applied indication is Combo 450 (binimetinib 45mg BID and encorafenib 450mg QD). Combo 450 (part 1, n=192) and Combo 300 (part 2, n=258) were compared post-hoc. Median PFS by BIRC was not statistically significantly longer with Combo 450 vs Combo 300 (14.9 months [95% CI 11.0, 18.5] vs 12.9 months [95% CI 10.1, 14.0]; HR 0.79 [95% CI 0.60, 1.03]; one-sided log-rank p=0.0845) at the cut-off dates for initial analysis (19 May 2016 and 9 November 2016, respectively). Combo 450 did not increase the proportion of confirmed responses (63.0% vs. 65.9%), although the median duration of confirmed response was longer (16.6 vs. 12.7 months, with overlapping confidence intervals). When Combo 450 and Combo 300 were compared at the same cut-off (9 November 2016) there had been an additional 5 PFS events in the Combo 450 arm; median PFS by BIRC was 15.5 vs. 12.9 months (stratified HR 0.77, 95% CI 0.58, 1.01; 2-sided log rank p value 0.0573). However as noted above, patients enrolled to part 2 of the trial seem to have a worse prognosis than those in part 1.

The confirmed response rate (CR + PR) was higher in the Combo 450 group (63.0%) compared with encorafenib (50.5%) and vemurafenib (40.3%). Confirmed ORR in the small subgroup of patients with prior first-line immunotherapy was lower but showed the same pattern as in the overall population; Combo 450 (N=8) 50.0%; encorafenib (N=11) 45.5%; vemurafenib (N=7) 28.6%. These were all partial responses, with no complete responses in this subgroup. The median time to response for responders in all treatment arms was short (1.9 – 2.1 months), which corresponds with the first post-baseline response assessment at Cycle 3 Day 1. The median duration of response (DOR) per BIRC, calculated for confirmed responses, was longer in the Combo 450 arm (16.6 months) in the Combo 450 arm than the encorafenib (14.9 months) or vemurafenib arms (12.3 months).

The PRO findings appeared supportive. The Functional Assessment of Cancer Therapy-Melanoma (FACT M), the European Organisation for Research and Treatment of Cancer's core quality of life questionnaire (EORTC QLQ C30) and the EuroQoL 5 Dimension 5 Level examination (EQ 5D 5L) were used to explore patient-reported outcomes (PRO) measures of health-related Quality of Life, functioning, melanoma symptoms, and treatment-related adverse reactions. A definitive 10% deterioration in FACT M and in EORTC QLQ-C30 was significantly delayed in patients treated with Combo 450 relative to other treatments. The median time to definitive 10% deterioration in the FACT-M score was not reached in the Combo 450 arm and was 22.1 months (95% CI: 15.2, NE) in the vemurafenib arm with a HR for the difference of 0.46 (95% CI: 0.29, 0.72). An analysis of time to definitive 10% deterioration in EORTC QLQ C30 score provided with similar results.

Patients receiving Combo 450 reported no change or a slight improvement in the mean change from baseline EQ 5D 5L index score at all visits, whilst patients receiving vemurafenib or encorafenib reported decreases at all visits (with statistical significant differences). An evaluation of change over time in score yielded the same trend for EORTC QLQ C30 and at all visit for FACT M).

The results from the Phase 2 study CLGX818X2109 provided preliminary support regarding the efficacy of Combo 450 in the treatment of BRAF V600 mutant melanoma. The overall response rate (confirmed ORR) of 69.3% was similar but the median PFS was shorter (14.9 months in Study CMEK162B2301 vs. 9.5 months in Study CLGX818X2109). This may be because the PFS data was not fully mature at the time of data cut off; median follow up time was 6.4 months compared to 16.7 months for the Combo 450 arm in the COLUMBUS trial. Tumour assessments were performed every 8 weeks in COLUMBUS compared to every 4 weeks in LOGIC 2.

Binimetinib is to be given in combination with encorafenib. For additional information on warnings and precautions associated with encorafenib treatment, see section 4.4 of encorafenib SmPC.

BRAF mutation testing

Before taking binimetinib in combination with encorafenib, patients must have BRAF V600 mutation confirmed by validated test. The efficacy and safety of binimetinib in combination with encorafenib have been established only in patients with tumours expressing BRAF V600E and V600K mutations. Binimetinib in combination with encorafenib should not be used in patients with wild type BRAF malignant melanoma.

Binimetinib in combination with encorafenib in patients who have progressed on a BRAF inhibitor

There are limited data for use of the combination of binimetinib with encorafenib in patients who have progressed on a prior BRAF inhibitor given for the treatment of unresectable or metastatic melanoma with BRAF V600 mutation. These data show that the efficacy of the combination would be lower in these patients.

Binimetinib in combination with encorafenib in patients with brain metastases

There are limited efficacy data with the combination of binimetinib and encorafenib in patients with a BRAF V600 mutant melanoma which have metastasised to the brain (see section 5.1).

The safety and efficacy of binimetinib in children and adolescents have not yet been established. No data are available. The European Medicines Agency has deferred the obligation to submit the results of studies with binimetinib in one or more subsets of the paediatric population in melanoma (see section 4.2 for information on paediatric use).

2.5.2. Conclusions on the clinical efficacy

Overall, Combo 450 demonstrates both a statistically significant and clinically meaningful benefit in PFS over the comparator vemurafenib as well as a clinically relevant benefit over encorafenib monotherapy at its maximally tolerated monotherapy dose of 300 mg QD. The OS results of Part I of the COLUMBUS study demonstrate a statistically significant benefit favouring the Combo 450 treatment over vemurafenib.

The combination therapy of binimetinib and encorafenib showed an improved efficacy compared to BRAF inhibitors given as monotherapies (vemurafenib and encorafenib) which is consistent with clinical data from other combination therapies of BRAF/MEK inhibition of patients with advanced or metastatic melanoma harbouring BRAF V600 mutations.

The CHMP requests the following measures to address issues related to efficacy:

- OS results for Combo 300 and updated Combo 300 PFS analysis, including more mature data for the Enco300 Part 2 arm.

2.6. Clinical safety

The safety data from a total of 864 patients were presented; 427 patients received binimetinib monotherapy and 437 patients received binimetinib in combination with encorafenib.

As of 20 January 2016, a total of 2555 healthy subjects and patients have received at least 1 dose of binimetinib. The specific combination of binimetinib plus encorafenib has been evaluated in 274 patients with metastatic melanoma at the recommended doses of 450 mg once daily [QD] encorafenib and 45 mg twice daily [BID] binimetinib (Combo 450), with 121 (44.2%) patients exposed to this combination for ≥48 weeks.

Data from 5 supportive clinical trials in patients with unresectable or metastatic melanoma were included for the safety evaluation of the combination of binimetinib and encorafenib for the treatment of patients with unresectable or metastatic *BRAF* V600-mutant melanoma (Figure 23):

• 3 clinical studies are pooled to summarise the safety of the combination

• 2 clinical studies are pooled to summarise the safety of binimetinib monotherapy.

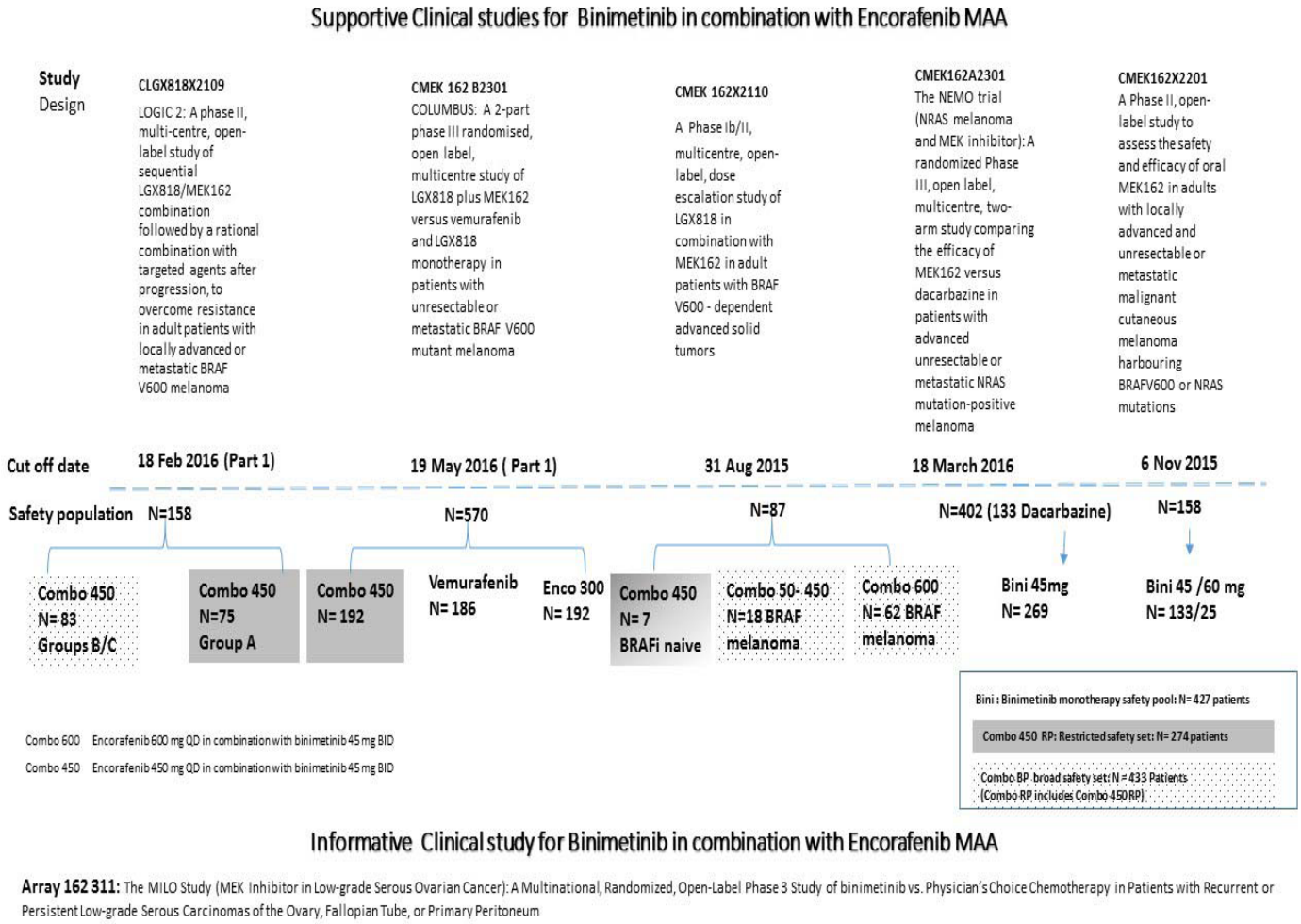


Figure 23: Supportive Clinical Trials for the Binimetinib and Encorafenib Combination

The safety data presented includes:

• The **binimetinib monotherapy safety pool**, which includes data from 427 patients with metastatic melanoma, who were previously naïve to MEK inhibitors and were enrolled at or randomised to a dose of 45 mg BID binimetinib (269 patients from Study CMEK162A2301 and 158 patients from Study CMEK162X2201).

• The **broad combination safety pool**, which includes pooled data from 437 patients with *BRAF* V600-mutant metastatic melanoma enrolled at or randomized to a dose of 45 mg BID binimetinib plus various doses of encorafenib, ranging from 400 mg QD to 600 mg QD (192 patients from Study CMEK162B2301 [Part 1], 158 patients from Study CLGX818X2109 and 87 patients from Study CMEK162X2110).

• The **restricted combination safety pool**, which includes data from 274 patients with *BRAF* V600-mutant metastatic melanoma enrolled at or randomized to a dose of 45 mg BID binimetinib plus 450 mg QD encorafenib (192 patients from Study CMEK162B2301 [Part 1], 75 patients from Study CLGX818X2109 [Group A] and 7 patients from Study CMEK162X2110) who were previously naïve to BRAF inhibitors (either as monotherapy or in combination with a MEK inhibitor).

Two displays are utilised:

• The **Broad Safety Set**, which includes columns for the binimetinib monotherapy safety pool, the broad combination safety pool, the restricted combination safety pool, and CMEK162B2301 Part 1 treatment arms (binimetinib in combination with encorafenib [Combo 450], encorafenib monotherapy [Enco 300] arm and vemurafenib arm).

• The **Restricted Safety Set**, which includes columns for the binimetinib monotherapy safety pool, the restricted combination safety pool and CMEK162B2301 Part 1 treatment arms (binimetinib in combination with Enco 300 arm, encorafenib monotherapy arm and vemurafenib arm).

In the pooled safety analyses

• **'Combo 450'** refers to the combination of binimetinib 45 mg BID and encorafenib 450 mg QD in Study CMEK162B2301 [Part 1]

• **'Combo RP'** refers to the restricted combination safety pool (patients who received doses of binimetinib at 45 mg BID in combination with encorafenib at 450 mg QD,

• '**Combo BP'** refers to the broad combination safety pool (who received doses of binimetinib at 45 mg BID in combination with encorafenib ranging from 400 mg to 600 mg QD).

• **'Bini P'** refers to the pooled binimetinib monotherapy population.

At the cut-off date for the studies with encorafenib+ binimetinib combination [CMEK162B2301 (09 Nov 2016), CLGX818X2109 (20 Dec 2016), CMEK162X2110 (31 Dec 2016)] and for binimetinib monotherapy [CMEK162B2301 Part 1 (09 Nov 2016), CLGX818X2101 Part 1 (18 Aug 2014), CLGX818X2102 (05 May 2015)], 83 of 274 (30.3%) patients and 37 of 217 patients (17.1%) remained on treatment in the Combo 450°RP and in the Enco 300°P, respectively.

Patient exposure

As of 20 January 2016, a total of 2555 subjects which comprises 220 healthy subjects, 164 patients with rheumatoid arthritis, 12 patients with hepatic dysfunction and 2159 patients with advanced cancer, have received at least 1 dose. The specific combination of binimetinib plus encorafenib has been evaluated in 274 patients with metastatic melanoma at the recommended doses of 45 mg BID binimetinib and 450 mg QD encorafenib (Combo 450).

The median duration of exposure was 11.7 months in patients treated with Combo 450, 7.1 months in patients treated with encorafenib 300 mg and 6.2 months in patients treated with vemurafenib.

In the Combo 450 RP population, the median relative dose intensity of encorafenib and binimetinib was 99.66% and 99.50%. The relative dose intensity in the Combo 450 RP population for encorafenib was 100% for 123 patients (44.9%) and 100% for binimetinib in 109 patients (39.8%).

The median relative dose intensity for encorafenib remained higher in the Combo 450 RP population compared to the Enco 300 P population (99.66% vs 84.98%) and a higher proportion of patients in the Combo 450 RP population had a relative dose intensity of 100% (44.9% vs 28.6%). The median relative dose intensity (RDI) for Combo 450 was 99.6 % for binimetinib and 100 % for encorafenib the median RDI was 86.2 % for Enco 300 and 94.5 % for vemurafenib.

Table 64: Duration of Exposure to Study Drug

	Melanoma				Study CMEK162B2301		
	Bini 45 mg BID N=427	Enco 300 mg QD N=217	Combo pooled doses N=433	Combo 450 mg QD N=274	Combo 450 mg QD N=192	Enco 300 mg QD N=192	Vemurafenib N=186
Duration of exposure (weeks) [1]							
n	427	217	433	274	192	192	186
Mean	18.91	40.44	41.96	48.90	54.32	42.42	35.94
SD	19.470	30.342	30.607	29.485	30.881	31.181	29.474
Median	13.00	29.71	34.00	41.93	51.21	31.36	27.14
Minimum	0.3	0.1	0.1	0.4	0.4	0.1	0.9
Maximum	183.33	113.3	132.9	128.7	116.0	113.3	121.6
Patient-months	1856.95	2018.30	4178.79	3081.43	2398.69	1872.89	1537.31
Exposure ≥48 weeks, n(%)	30 (7.00)	77 (35.5)	157 (36.3)	121 (44.2)	101 (52.6)	75 (39.1)	47 (25.3)

Source: ISS Table 1.5.1.1

[1] Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.

Adverse events

Table 65 presents an overall summary of AEs and deaths for the Broad Safety Set.

Table 65: Death and Overall Summary of Adverse Events by Treatment (Broad Safety Set)

	Melanoma				Study CMEK162B2301		
	Bini 45mg BID N=427 n (%)	Enco 300mg QD N=217 n (%)	Combo pooled doses N=433 n (%)	Combo 450mg QD N=274 n (%)	Combo 450mg QD N=192 n (%)	Enco 300mg QD N=192 n (%)	Vemurafenib N=186 n (%)
On-treatment deaths [1]	46 (10.8)	15 (6.5)	44 (10.2)	23 (8.4)	17 (8.9)	14 (7.3)	19 (10.2)
Adverse events (AEs)							
All grades	427 (100)	216 (99.5)	426 (98.4)	271 (98.9)	189 (98.4)	191 (99.5)	185 (99.5)
Grades 3/4	285 (66.7)	146 (67.3)	254 (58.7)	159 (58.0)	111 (57.8)	127 (66.1)	118 (63.4)
Suspected to be drug-related							
All grades	414 (97)	216 (99.5)	386 (89.1)	246 (89.8)	169 (89.8)	191 (99.5)	180 (96.8)
Grades 3/4	209 (48.9)	109 (50.2)	142 (32.8)	91 (33.2)	69 (35.9)	95 (49.5)	85 (45.7)
Serious adverse events							
All grades	141 (33)	69 (31.8)	158 (36.5)	98 (35.8)	66 (34.4)	65 (33.9)	69 (37.1)
Grades 3/4	116 (27.2)	58 (26.7)	142 (32.8)	87 (31.8)	57 (29.7)	54 (28.1)	60 (32.3)
Suspected to be drug-related							
All grades	52 (12.2)	34 (15.7)	45 (10.4)	28 (10.2)	21 (10.9)	33 (17.2)	25 (13.4)
Grades 3/4	44 (10.3)	25 (11.5)	34 (7.9)	21 (7.7)	15 (7.8)	24 (12.5)	22 (11.8)
AEs leading to treatment discontinuation							
All grades	103 (24.1)	38 (17.5)	45 (10.4)	28 (10.2)	24 (12.5)	27 (14.1)	31 (16.7)
Grades 3/4	70 (16.4)	29 (13.4)	33 (7.6)	24 (8.8)	22 (11.5)	21 (10.9)	18 (9.7)
Suspected to be drug-related							
All grades	82 (19.2)	28 (12.9)	26 (6.0)	13 (4.7)	12 (6.3)	19 (9.9)	26 (14.0)
Grades 3/4	54 (12.6)	22 (10.1)	15 (3.5)	10 (3.6)	10 (5.2)	16 (8.3)	13 (7.0)
AEs requiring dose interruption and/or change							
All grades	285 (66.7)	152 (70.0)	212 (49.0)	129 (47.1)	92 (47.9)	135 (70.3)	114 (61.3)
Grades 3/4	176 (41.2)	93 (42.9)	139 (32.1)	88 (32.1)	63 (32.8)	85 (44.3)	71 (38.2)
Suspected to be drug-related							
All grades	253 (59.3)	136 (62.7)	169 (39.0)	109 (39.8)	81 (42.2)	121 (63.0)	106 (57.0)
Grades 3/4	145 (34)	83 (38.2)	103 (23.8)	65 (23.7)	52 (27.1)	75 (39.1)	57 (30.6)
AEs requiring additional therapy [2]							
All grades	394 (92.3)	205 (94.5)	364 (84.1)	236 (86.1)	165 (85.9)	181 (94.3)	171 (91.9)
Grades 3/4	163 (38.2)	120 (55.3)	160 (37.0)	101 (36.9)	67 (34.9)	106 (55.2)	91 (48.9)
Suspected to be drug-related							
All grades	364 (85.2)	198 (91.2)	268 (61.9)	171 (62.4)	117 (60.9)	174 (90.6)	159 (85.5)
Grades 3/4	99 (23.2)	89 (41)	54 (12.5)	37 (13.5)	25 (13.0)	79 (41.1)	56 (30.1)

Source: ISS Table 2.2.1
[1] Deaths occurring >30 days after end of treatment are not included.
[2] Additional therapy includes all non-drug therapy and concomitant medications.
A patient is counted once within each category.
MedDRA Version 19.0 has been used for the reporting of adverse events.

Adverse Events by System Organ Class (SOC)

Table 66 presents a summary of AEs, regardless of relationship to study drug, by SOC, and reported in ≥20% of patients in any study population under each SOC (overall and maximum Grade 3/4) for the Broad Safety Set.

Table 66: Adverse Events, Regardless of Study Drug Relationship, by Primary System Organ Class by Treatment – Overall and Maximum Grade 3 or 4 (≥20% in any population) (Broad Safety Set)

	Melanoma				Study CMEK162B2301		
Primary System Organ Class Preferred Term Grades	Bini 45mg BID N=427 n (%)	Enco 300mg QD N=217 n (%)	Combo pooled doses N=433 n (%)	Combo 450mg QD N=274 n (%)	Combo 450mg QD N=192 n (%)	Enco 300mg QD N=192 n (%)	Vemurafenib N=186 n (%)
Any primary system organ class							
All grades	427 (100)	216 (99.5)	426 (98.4)	271 (98.9)	189 (98.4)	191 (99.5)	185 (99.5)
Grades 3/4	283 (66.3)	146 (67.3)	254 (58.7)	159 (58.0)	111 (57.8)	127 (66.1)	118 (63.4)
Blood and lymphatic system disorders							
All grades	62 (14.5)	26 (12.0)	96 (22.2)	63 (23.0)	40 (20.8)	20 (10.4)	30 (16.1)
Grades 3/4	20 (4.7)	11 (5.1)	30 (6.9)	17 (6.2)	11 (5.7)	9 (4.7)	9 (4.8)
Eye disorders							
All grades	237 (55.5)	58 (26.7)	252 (57.7)	158 (57.7)	104 (54.2)	53 (27.6)	62 (33.3)
Grades 3/4	16 (3.7)	1 (0.5)	12 (2.8)	6 (2.2)	5 (2.6)	1 (0.5)	1 (0.5)
Gastrointestinal disorders							
All grades	305 (71.4)	151 (69.6)	320 (73.9)	201 (73.4)	138 (71.9)	130 (67.7)	127 (68.3)
Grades 3/4	39 (9.1)	26 (12.0)	58 (13.4)	35 (12.8)	22 (11.5)	25 (13.0)	19 (10.2)
General disorders and administration site conditions							
All grades	320 (74.9)	138 (63.6)	266 (61.3)	168 (61.3)	122 (63.5)	123 (64.1)	130 (69.9)
Grades 3/4	45 (10.5)	25 (11.5)	44 (10.2)	28 (10.2)	24 (12.5)	21 (10.9)	24 (12.9)
Infections and infestations							
All grades	175 (41.0)	92 (42.4)	192 (44.3)	137 (50)	97 (50.5)	82 (42.7)	92 (49.5)
Grades 3/4	32 (7.5)	7 (3.2)	33 (7.6)	25 (9.1)	19 (9.9)	6 (3.1)	9 (4.8)
Investigations							
All grades	268 (62.8)	82 (37.8)	244 (56.4)	156 (56.9)	103 (53.6)	71 (37.0)	77 (41.4)
Grades 3/4	130 (30.4)	20 (9.2)	96 (22.2)	61 (22.3)	47 (24.5)	17 (8.9)	14 (7.5)
Metabolism and nutrition disorders							
All grades	87 (20.4)	75 (34.6)	124 (28.6)	62 (22.6)	44 (22.9)	61 (31.8)	49 (26.3)
Grades 3/4	20 (4.7)	18 (8.3)	33 (7.6)	14 (5.1)	10 (5.2)	14 (7.3)	10 (5.4)
Musculoskeletal and connective tissue disorders							
All grades	157 (36.8)	172 (79.3)	237 (54.5)	150 (54.7)	102 (53.1)	149 (77.6)	125 (67.2)
Grades 3/4	20 (4.7)	46 (21.2)	17 (3.9)	12 (4.4)	5 (2.6)	43 (22.4)	19 (10.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)							
All grades	22 (5.2)	83 (38.2)	88 (20.6)	60 (21.9)	44 (22.9)	72 (37.5)	82 (44.1)
Grades 3/4	5 (1.2)	13 (6.0)	13 (3.0)	6 (2.2)	5 (2.6)	11 (5.7)	22 (11.8)
Nervous system disorders							
All grades	133 (31.1)	126 (58.1)	190 (43.9)	129 (47.1)	95 (49.5)	107 (55.7)	77 (41.4)
Grades 3/4	17 (4.0)	20 (9.2)	34 (7.9)	26 (9.5)	18 (9.4)	18 (9.4)	14 (7.5)
Psychiatric disorders							
All grades	45 (10.3)	78 (35.9)	76 (17.6)	53 (19.3)	42 (21.9)	64 (33.3)	31 (16.7)
Grades 3/4	3 (0.7)	8 (3.7)	7 (1.6)	5 (1.8)	3 (1.6)	6 (3.1)	0
Respiratory, thoracic and mediastinal disorders							
All grades	119 (27.9)	57 (26.3)	134 (30.9)	76 (27.7)	57 (29.7)	52 (27.1)	50 (26.9)
Grades 3/4	20 (4.7)	10 (4.6)	16 (3.7)	9 (3.3)	8 (4.2)	10 (5.2)	8 (4.3)
Skin and subcutaneous tissue disorders							
All grades	375 (87.8)	207 (95.4)	255 (58.9)	174 (63.5)	125 (65.1)	184 (95.8)	170 (91.4)
Grades 3/4	37 (8.7)	49 (22.6)	10 (2.3)	7 (2.6)	6 (3.1)	43 (22.4)	38 (20.4)
Vascular disorders							
All grades	98 (23.0)	43 (19.8)	87 (20.1)	52 (19.0)	36 (18.8)	36 (18.8)	36 (19.4)
Grades 3/4	44 (10.3)	7 (3.2)	22 (5.1)	17 (6.2)	12 (6.3)	7 (3.6)	6 (3.2)

Source: ISS Table 2.2.2.1
A patient is counted once within each preferred term and system organ class.
System organ classes are presented in alphabetical order. MedDRA Version 19.0 has been used for the reporting of adverse events.

Bini P vs Combo 450 RP (pooled sets)

The overall incidence of AEs and SAEs was similar between the Combo 450 RP population and Bini P population but a lower proportion of patients in the Combo 450 RP population reported Grade 3/4 AEs (58% vs 66.3%). In addition, in the Combo 450 RP population, a lower proportion of patients compared to the Bini P population reported AEs leading to treatment discontinuation, AEs requiring dose interruption or additional therapy (discontinuation: 10.2% vs 22.5%; interruption: 47.1% vs 66.3%, additional therapy 86.1%vs 92.3%). On-treatment deaths were reported in a similar proportion of patients in both arms.

In the Bini P population, the maximum reported severity of AEs was Grade 1, 2, 3 and 4 for 6.1%, 27.2%, 53.6% and 13.1% of patients, respectively. In the Combo 450 RP population, the maximum

reported severity of AEs was Grade 1, 2, 3 and 4 for 10.2%, 30.7%, 48.2% and 9.9% of patients, respectively, indicating less Grade 3 AEs (5.4% difference) than in the Bini P population.

The median time to onset of first Grade ¾ AEs was longer in the combo 450 RP population than in the Bini P population (2.6 months (95% CI: 1.8, 3.2) vs 1.0 month (95% CI: 0.9, 1.3)) (Figure OS 1):

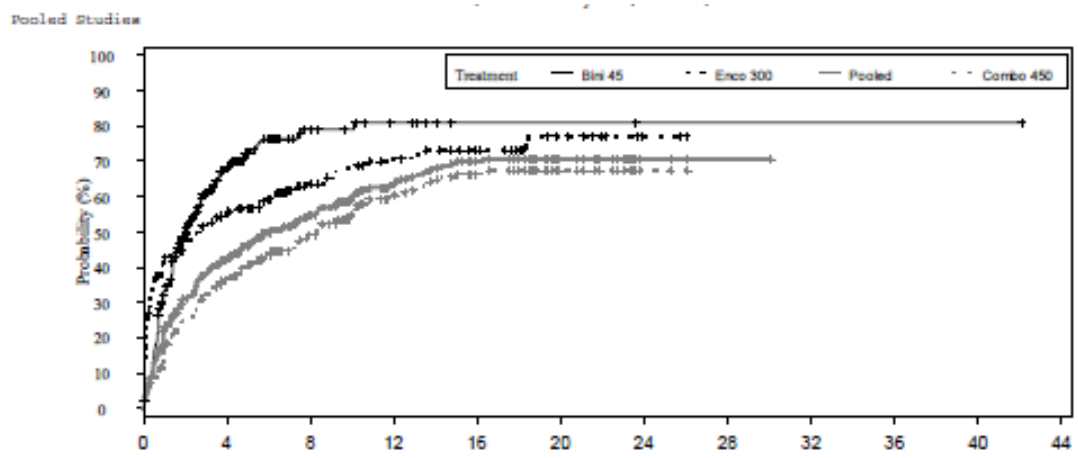


Figure 24: Kaplan-Meier-Plot of time to first adverse event grade ¾ (pooled studies)

AEs reported in ≥50% of patients in the Combo 450 RP population and at a higher incidence (≥10% difference) as compared to the Bini P population were reported under the SOC of musculoskeletal and connective tissue disorders (54.7% vs 36.8%). No Grade 3/4 AEs reported in ≥10% of patients in the Combo 450 RP population were reported under any SOC at a higher incidence as compared to the Bini P population (≥5% difference).

AEs reported in ≥50% of patients in the Bini P population and at a higher incidence as compared to the Combo 450 RP population (≥10% difference) were reported under the SOCs of skin and subcutaneous tissue conditions (74.9% vs 61.3%) and general and administrative site conditions (74.7% vs 60.9%). Grade 3/4 AEs reported in ≥10% of patients in the Bini P population and at a higher incidence as compared to the Combo 450 RP population (≥5% difference) were reported under the SOC of investigations (30.4% vs 22.3%).

Adverse Events by Preferred Term

Table 67 presents a summary of AEs, regardless of relationship to study drug that were reported for ≥10% of patients in any study population by PT (overall and maximum Grade 3/4) for the Broad Safety Set.

Table 67: Adverse Events, Regardless of Study Drug Relationship, by Preferred Term and Treatment – Overall and Maximum Grade 3 or 4 (≥10% in any population) (Broad Safety Set)

	Melanoma				Study CMEK162B2301																			
	Bini 45 mg N=427				Enco 300 mg N=217				Combo pooled doses N=269				Combo 450 mg N=274				Combo 450 mg N=192				Enco 300 mg N=192				Vemurafenib N=186			
	All grades		Grade 3/4		All grades		Grade 3/4		All grades		Grade 3/4		All grades		Grade 3/4		All grades		Grade 3/4		All grades		Grade 3/4		All grades		Grade 3/4	
Preferred term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total	427	100.0	283	66.3	216	99.5	146	67.3	426	98.4	254	58.7	271	98.9	159	58.0	189	98.4	111	57.8	191	99.5	127	66.1	185	99.5	118	63.4
Nausea	128	30	5	1.2	82	37.8	8	3.7	178	41.1	16	3.7	108	39.4	7	2.6	79	41.1	3	1.6	74	38.5	8	4.2	63	33.9	3	1.6
Diarrhoea	182	42.6	8	1.9	27	12.4	3	1.4	161	37.2	13	3.0	99	36.1	9	3.3	70	36.5	5	2.6	26	13.5	3	1.6	63	33.9	4	2.2
Fatigue	114	26.7	15	3.5	60	27.6	4	1.8	135	31.2	10	2.3	83	30.3	6	2.2	55	28.6	4	2.1	48	25.0	1	0.5	57	30.6	4	2.2
Vomiting	84	19.7	8	1.9	58	26.7	9	4.1	123	28.4	14	3.2	73	26.6	6	2.2	57	29.7	3	1.6	52	27.1	9	4.7	28	15.1	2	1.1
Arthralgia	31	7.3	1	0.2	93	42.9	20	9.2	100	23.1	5	1.2	68	24.8	2	0.7	49	25.5	1	0.5	84	43.8	18	9.4	83	44.6	11	5.9
Blood CK increased	191	44.7	89	20.8	2	0.9	0	0.0	93	21.5	22	5.1	68	24.8	15	5.5	44	22.9	13	6.8	2	1.0	0	0.0	4	2.2	0	0.0
Constipation	65	15.2	2	0.5	35	16.1	0	0.0	94	21.7	0	0.0	62	22.6	0	0.0	42	21.9	0	0.0	27	14.1	0	0.0	12	6.5	1	0.5
Headache	25	5.9	1	0.2	61	28.1	6	2.8	74	17.1	6	1.4	54	19.7	4	1.5	42	21.9	3	1.6	52	27.1	6	3.1	35	18.8	1	0.5
Anaemia	41	9.6	10	2.3	15	6.9	5	2.3	76	17.6	22	5.1	47	17.2	12	4.4	29	15.1	8	4.2	11	5.7	5	2.6	14	7.5	4	2.2
Abdominal pain	37	8.7	3	0.7	13	6.0	4	1.8	70	16.2	8	1.8	44	16.1	5	1.8	32	16.7	5	2.6	13	6.8	4	2.1	12	6.5	1	0.5
Pyrexia	53	12.4	0	0.0	31	14.3	2	0.9	82	18.9	11	2.5	43	15.7	7	2.6	35	18.2	7	3.6	29	15.1	2	1.0	52	28.0	0	0.0
Vision blurred	28	6.6	1	0.2	5	2.3	0	0.0	67	15.5	2	0.5	42	15.3	1	0.4	30	15.6	0	0.0	4	2.1	0	0.0	4	2.2	0	0.0
Alopecia	42	9.8	0	0.0	122	56.2	0	0.0	50	11.5	0	0.0	38	13.9	0	0.0	26	13.5	0	0.0	107	55.7	0	0.0	68	36.6	0	0.0
Asthenia	60	14.1	8	1.9	42	19.4	6	2.8	47	10.9	5	1.2	38	13.9	3	1.1	35	18.2	3	1.6	37	19.3	5	2.6	34	18.3	8	4.3
GGT increased	15	3.5	6	1.4	23	10.6	10	4.6	44	10.2	26	6.0	38	13.9	22	8.0	29	15.1	18	9.4	21	10.9	9	4.7	21	11.3	6	3.2
Myalgia	42	9.8	5	1.2	64	29.5	20	9.2	55	12.7	1	0.2	36	13.1	1	0.4	26	13.5	0	0.0	54	28.1	19	9.9	34	18.3	1	0.5
Dry skin	45	10.5	0	0.0	68	31.3	0	0.0	57	13.2	0	0.0	35	12.8	0	0.0	27	14.1	0	0.0	58	30.2	0	0.0	42	22.6	0	0.0
ALT increased	41	9.6	10	2.3	11	5.1	2	0.9	63	14.5	23	5.3	35	12.8	13	4.7	21	10.9	10	5.2	10	5.2	2	1.0	14	7.5	3	1.6
Hyperkeratosis	9	2.1	0	0.0	89	41.0	10	4.6	44	10.2	1	0.2	34	12.4	1	0.4	27	14.1	1	0.5	72	37.5	7	3.6	54	29.0	0	0.0
Rash	146	34.2	13	3.0	47	21.7	4	1.8	58	13.4	2	0.5	33	12.0	2	0.7	27	14.1	2	1.0	41	21.4	4	2.1	54	29.0	6	3.2
Oedema peripheral	174	40.7	3	0.7	19	8.8	0	0.0	54	12.5	2	0.5	33	12.0	2	0.7	20	10.4	2	1.0	15	7.8	0	0.0	20	10.8	1	0.5
Dizziness	25	5.9	0	0.0	10	4.6	0	0.0	46	10.6	3	0.7	31	11.3	3	1.1	24	12.5	3	1.6	9	4.7	0	0.0	5	2.7	0	0.0
Hypertension	64	15	34	8.0	11	5.1	6	2.8	43	9.9	18	4.2	31	11.3	16	5.8	21	10.9	11	5.7	11	5.7	6	3.1	21	11.3	6	3.2
Muscle spasms	5	1.2	0	0.0	6	2.8	0	0.0	43	9.9	0	0.0	31	11.3	0	0.0	17	8.9	0	0.0	6	3.1	0	0.0	4	2.2	0	0.0
Nasopharyngitis	21	4.9	0	0.0	11	5.1	0	0.0	34	7.9	0	0.0	28	10.2	0	0.0	20	10.4	0	0.0	11	5.7	0	0.0	18	9.7	0	0.0
Pain in extremity	25	5.9	3	0.7	45	20.7	2	0.9	48	11.1	5	1.2	27	9.9	4	1.5	21	10.9	2	1.0	42	21.9	2	1.0	25	13.4	2	1.1
AST increased	59	13.8	9	2.1	8	3.7	1	0.5	54	12.5	15	3.5	26	9.5	6	2.2	16	8.3	4	2.1	8	4.2	1	0.5	15	8.1	3	1.6
Retinopathy	22	5.2	0	0.0	1	0.5	0	0.0	46	10.6	2	0.5	26	9.5	0	0.0	4	2.1	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0
Abdom. pain upper	23	5.4	2	0.5	20	9.2	2	0.9	30	6.9	3	0.7	25	9.1	2	0.7	23	12.0	2	1.0	18	9.4	2	1.0	17	9.1	1	0.5
Pruritus	58	13.6	4	0.9	47	21.7	1	0.5	42	9.7	1	0.2	25	9.1	1	0.4	21	10.9	1	0.5	42	21.9	1	0.5	20	10.8	0	0.0
Back pain	26	6.1	1	0.2	33	15.2	5	2.3	44	10.2	2	0.5	24	8.8	2	0.7	18	9.4	1	0.5	29	15.1	5	2.6	11	5.9	3	1.6

	Melanoma				Study CMEK162B2301																			
	Bini 45 mg N=427				Enco 300 mg N=217				Combo pooled doses N=269				Combo 450 mg N=274				Combo 450 mg N=192				Enco 300 mg N=192				Vemurafenib N=186			
	All grades		Grade 3/4		All grades		Grade 3/4		All grades		Grade 3/4		All grades		Grade 3/4		All grades		Grade 3/4		All grades		Grade 3/4		All grades		Grade 3/4	
Preferred term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
PP keratoderma	2	0.5	0	0.0	50	23.0	4	1.8	23	5.3	0	0.0	21	7.7	0	0.0	17	8.9	0	0.0	49	25.5	3	1.6	29	15.6	2	1.1
Cough	28	6.6	0	0.0	18	8.3	1	0.5	46	10.6	1	0.2	21	7.7	1	0.4	16	8.3	1	0.5	17	8.9	1	0.5	13	7.0	1	0.5
Insomnia	23	5.4	0	0.0	48	22.1	6	2.8	27	6.2	0	0.0	20	7.3	0	0.0	18	9.4	0	0.0	35	18.2	5	2.6	15	8.1	0	0.0
Decreased appetite	55	12.9	2	0.5	48	22.1	1	0.5	40	9.2	2	0.5	20	7.3	0	0.0	16	8.3	0	0.0	40	20.8	1	0.5	36	19.4	2	1.1
Retinal detachment	44	10.3	0	0.0	1	0.5	0	0.0	21	4.8	2	0.5	18	6.6	1	0.4	15	7.8	1	0.5	1	0.5	0	0.0	1	0.5	0	0.0
Dyspnoea	44	10.3	6	1.4	13	6.0	1	0.5	38	8.8	4	0.9	18	6.6	1	0.4	14	7.3	1	0.5	9	4.7	1	0.5	16	8.6	3	1.6
EF decreased	44	10.3	15	3.5	4	1.8	2	0.9	26	6.0	3	0.7	18	6.6	2	0.7	11	5.7	2	1.0	4	2.1	2	1.0	1	0.5	0	0
Erythema	30	7.0	1	0.2	30	13.8	1	0.5	21	4.8	0	0.0	18	6.6	0	0.0	13	6.8	0	0.0	24	12.5	1	0.5	31	16.7	1	0.5
Skin papilloma	0	-	0	0.0	20	9.2	0	0.0	19	4.4	0	0.0	17	6.2	0	0.0	12	6.3	0	0.0	18	9.4	0	0.0	31	16.7	0	0.0
Dysgeusia	38	8.9	0	0.0	26	12.0	0	0.0	25	5.8	0	0.0	17	6.2	0	0.0	10	5.2	0	0.0	22	11.5	0	0.0	16	8.6	0	0.0
PPE syndrome	5	1.2	1	0.2	112	51.6	27	12.4	19	4.4	0	0.0	16	5.8	0	0.0	13	6.8	0	0.0	98	51.0	26	13.5	26	14.0	2	1.1
Musculoskeletal pain	6	1.4	0	0.0	36	16.6	6	2.8	28	6.5	0	0.0	16	5.8	0	0.0	11	5.7	0	0.0	32	16.7	6	3.1	11	5.9	2	1.1
Dermatitis acneiform	177	41.5	11	2.6	9	4.1	0	0.0	13	3.0	0	0.0	10	3.6	0	0.0	5	2.6	0	0.0	8	4.2	0	0.0	8	4.3	0	0.0
Keratosis pilaris	0	-	0	0.0	35	16.1	0	0.0	10	2.3	0	0.0	9	3.3	0	0.0	9	4.7	0	0.0	33	17.2	0	0.0	43	23.1	0	0.0
Weight decreased	21	4.9	1	0.2	34	15.7	3	1.4	16	3.7	0	0.0	9	3.3	0	0.0	6	3.1	0	0.0	29	15.1	2	1.0	20	10.8	0	0.0
Photosensitivity reaction	4	0.9	0	0.0	7	3.2	0	0.0	13	3.0	1	0.2	8	2.9	1	0.4	8	4.2	1	0.5	7	3.6	0	0.0	45	24.2	2	1.1
Keratoacanthoma	0	-	0	0.0	12	5.5	0	0.0	6	1.4	0	0.0	6	2.2	0	0.0	4	2.1	0	0.0	12	6.3	0	0.0	21	11.3	6	3.2
Pain	3	0.7	1	0.2	12	5.5	7	3.2	7	1.6	2	0.5	6	2.2	2	0.7	3	1.6	1	0.5	12	6.3	7	3.6	3	1.6	0	0.0
Rash maculo-papular	25	5.9	3	0.7	26	12.0	3	1.4	12	2.8	0	0.0	6	2.2	0	0.0	3	1.6	0	0.0	18	9.4	1	0.5	27	14.5	8	4.3
Rash generalised	10	2.3	0	0.0	12	5.5	1	0.5	5	1.2	1	0.2	4	1.5	0	0.0	4	2.1	0	0.0	12	6.3	1	0.5	17	9.1	8	4.3
Stomatitis	19	4.4	5	1.2	15	6.9	1	0.5	6	1.4	0	0.0	4	1.5	0	0.0	4	2.1	0	0.0	15	7.8	1	0.5	11	5.9	1	0.5
Xerosis	19	4.4	0	0.0	16	7.4	0	0.0	5	1.2	0	0.0	4	1.5	0	0.0	4	2.1	0	0.0	16	8.3	0	0.0	8	4.3	0	0.0
Melanocytic naevus	1	0.2	0	0.0	23	10.6	0	0.0	8	1.8	0	0.0	4	1.5	0	0.0	3	1.6	0	0.0	18	9.4	0	0.0	7	3.8	0	0.0
Skin hyper pigmentation	0	-	0	0.0	16	7.4	0	0.0	3	0.7	0	0.0	3	1.1	0	0.0	3	1.6	0	0.0	15	7.8	0	0.0	3	1.6	0	0.0
Facial paralysis	0	-	0	0.0	12	5.5	3	1.4	3	0.7	1	0.2	2	0.7	1	0.4	2	1.0	1	0.5	10	5.2	3	1.6	1	0.5	0	0.0
Rash papular	13	3.0	1	0.2	12	5.5	0	0.0	3	0.7	0	0.0	2	0.7	0	0.0	2	1.0	0	0.0	10	5.2	0	0.0	6	3.2	0	0.0
Skin exfoliation	4	0.9	0	0.0	12	5.5	0	0.0	2	0.5	0	0.0	1	0.4	0	0.0	1	0.5	0	0.0	11	5.7	0	0.0	4	2.2	0	0.0
Sunburn	2	0.5	0	0.0	1	0.5	0	0.0	1	0.2	0	0.0	1	0.4	0	0.0	0	0.0	0	0.0	1	0.5	0	0.0	19	10.2	1	0.5

Source: ISS Table 2.2.3

A patient is counted once within each preferred term.

Preferred terms are sorted in descending frequency in the 'Combo 450mg-melanoma' column

MedDRA Version 19.0 has been used for the reporting of adverse events.

Abd. pain upper =Abdominal pain upper, Blood CK increased = Blood creatine phosphokinase increased; GGT increased = Gamma-glutamyl transferase increased; ALT increased = Alanine aminotransferase increased, AST increased = Aspartate aminotransferase increased; EF = Ejection fraction; PP keratoderma = Palmoplantar keratoderma; PPE syndrome = Palmar-plantar erythrodysaesthesia syndrome

Relationship of Adverse Events to Study Treatment

The relationship of study treatment to each AE (suspected or not suspected) was evaluated by the investigator and treatment-related AEs that were reported for ≥20% of patients in any study population by PT (overall and maximum Grade 3/4) for the Broad Safety Set are summarised below.

Bini P vs Combo 450 RP (pooled sets)

The overall incidence of treatment-related AEs and Grade 3/4 AEs was lower in the Combo 450 RP population than the Bini P population (AEs: 89.8% vs 97%; Grade 3/4 AEs: 33.2% vs 48.9%).

In the Bini P population, treatment-related AEs reported in ≥20% of patients were blood CK increased (42.2%), diarrhoea (33.5%), rash (32.8%) and nausea (21.3%). The only treatment related Grade 3/4 adverse event reported in ≥5% of patients was blood CK increased (20.4%).

In the Combo 450 RP population, treatment-related AEs reported in ≥20% of patients were nausea (29.6%), diarrhoea (27%), fatigue (25.5%) and blood CK increased (22.6%). The only treatment related Grade 3/4 AE reported in ≥5% of patients was GGT increased (6.2%).

Treatment-related AEs reported at a higher incidence in the Combo 450 RP population than the Bini P population (≥10% difference) were arthralgia (16.1% vs 3.5%). GGT increased, the only treatment-related Grade 3/4 AE reported in ≥5% of patients in the Combo 450 RP population was reported at a higher incidence compared to the Bini P population (6.2% vs 0.2%).

Treatment-related AEs reported at a higher incidence in the Bini P population than the Combo 450 RP population (≥10% difference) were blood CK increased (42.2% vs 22.6%), diarrhoea (33.5% vs 27%) and rash (32.8% vs 10.2%). The only treatment-related Grade 3/4 AE reported in ≥5% of patients were blood CK increased, which was also reported at a higher incidence compared to the Combo 450 RP population (20.4% vs 4%).

4-month update

As of the 4-month safety update, the incidence of AEs assessed by the Investigator as related to study treatment was generally consistent with the trends observed in summaries of all-cause AEs by treatment group and to that previously reported for the same population in the initial.

The overall incidence of treatment-related AEs and Grade 3/4 AEs at the 4-month safety update remained lower in the Combo 450 RP population compared to the Enco 300 P population (AEs: 98.9% vs 99.5%; Grade 3/4 AE: 61.3% vs 67.7%). The only relevant changes for incidences of individual AEs since the initial MAA were in the Combo 450 RP population: Arthralgia (27% vs 24.8%), Blood creatine phosphokinase (CK) increased (27.0% vs 24.8%) and back pain (10.9% vs 8.8%).

Table 68: Adverse Reactions Occurring in Metastatic Melanoma Patients Receiving

System Organ Class	Adverse reaction	Frequency (All grades)	Grade3/4 (%)
Infections and infestations	Skin infection	Very common	4
Nervous system	Dropped head syndrome[b]	Uncommon	0
Eye disorder	RPED	Very common	1
	Visual impairment		Below 1
	Increased intraocular pressure including glaucoma	Common	0
	Retinal vein occlusion		1
Cardiac disorders	Left ventricular dysfunction	Very common	4
	Bradycardia	Common	0
Vascular disorders	Hypertension	Very common	8
	Venous thromboembolism	Common	2
	Haemorrhage[f]		2
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Very common	2
	Pneumonitis	Common	Below 1
Gastrointestial disorders	Diarrhoea	Very common	2
	Vomiting		2
	Nausea		1
	Dry mouth	Common	0
	Stomatitis[g]		2
Skin and subcutaneous tissue disorders	Rash[h]	Very common	4
	Acneiform dermatitis		3
	Pruritus		1

	Dry skin		0
	Alopecia	Common	0
	Skin fissures		0
Musculoskeletal and connective tissue	Myopathy[i]	Very common	2
	Rhabdomyolysis	Uncommon	Below 1
Renal and urinary	Renal failure	Common	Below 1
General disorders and administration site conditions	Peripheral oedema[j]	Very common	Below 1
	Periorbital oedema, eye oedema, eyelid oedema		Below 1
	Face oedema	Common	Below 1
Investigations	Blood creatine phosphokinase increased	Very common	21
	Aspartate aminotransferase increased		2
	Alanine aminotransferase increased	Common	2
	Hypokalaemia		2
	Hypoalbuminaemia		Below 1
	Blood creatinine increased		0

Table 69: Adverse reactions occurring in patients receiving binimetinib in combination with encorafenib at the recommended dose (n = 274)

System Organ Class	Adverse reaction	Frequency (All grades) n (%)	Frequency (Grade 3-4) n (%)
Neoplasms benign, malignant and unspecified	Cutaneous squamous cell carcinoma[a]	9 (3.3)	1 (0.4)
	Basal cell carcinoma[*]	3 (1.1)	0
	Skin papilloma[*]	22 (8.0)	0
Blood and lymphatic system disorders	Anaemia	54 (19.7)	13 (4.7)
Immune system disorders	Hypersensitivity[b]	9 (3.3)	0
Nervous system disorders	Neuropathy peripheral[*]	36 (13.1)	3 (1.1)
	Dizziness[*]	42 (15.3)	7 (2.6)
	Headache[*]	59 (21.5)	4 (1.5)
	Dysgeusia	18 (6.6)	0
	Facial paresis[c]	2 (0.7)	1 (0.4)
Eye disorders	Visual impairment[*]	59 (21.5)	1 (0.4)
	RPED[*]	81 (29.6)	5 (1.8)
	Uveitis[*]	12 (4.4)	1 (0.4)
Cardiac disorders	Left ventricular dysfunction[d]	23 (8.4)	3 (1.1)
Vascular disorders	Haemorrhage[e]	49 (17.9)	9 (3.3)
	Hypertension[*]	32 (11.7)	15 (5.5)
	Venous thromboembolism[f]	13 (4.7)	3 (1.1)

Gastrointestinal disorders	Abdominal pain*	75 (27.4)	7 (2.6)
	Diarrhoea*	104 (38.0)	9 (3.3)
	Vomiting*	77 (28.1)	6 (2.2)
	Nausea	114 (41.6)	7 (2.6)
	Constipation	66 (24.1)	0
	Colitis[g]	6 (2.2)	2 (0.7)
	Pancreatitis*	2 (0.7)	2 (0.7)
Skin and subcutaneous tissue disorders	Hyperkeratosis *	57 (20.8)	1 (0.4)
	Rash *	54 (19.7)	2 (0.7)
	Dry skin*	40 (14.6)	0
	Pruritus*	32 (11.7)	1 (0.4)
	Alopecia*	40 (14.6)	0
	Photosensitivity*	11 (4.0)	1 (0.4)
	Dermatitis acneiform*	12 (4.4)	0
	Palmar-plantar erythrodysaesthesia syndrome (PPES)	17 (6.2)	0
	Erythema*	22 (8.0)	0
	Panniculitis*	4 (1.5)	0
Musculoskeletal and connective tissue disorders	Arthralgia*	74 (27.0)	2 (0.7)
	Muscular disorders/Myalgia[h]	71 (25.9)	2 (0.7)
	Back pain	30 (10.9)	2 (0.7)
	Pain in extremity	29 (10.6)	4 (1.5)
	Rhabdomyolysis	1 (0.4)	1 (0.4)
Renal and urinary disorders	Renal failure*	9 (3.3)	6 (2.2)
General disorders and administration site conditions	Pyrexia*	47 (17.2)	8 (2.9)
	Peripheral oedema [i]	42 (15.3)	3 (1.1)
	Fatigue*	120 (43.8)	8 (2.9)
Investigations	Blood creatine phosphokinase increased	74 (27.0)	16 (5.8)
	Transaminase increased*	43 (15.7)	15 (5.5)
	Gamma-glutamyl transferase increased*	40 (14.6)	23 (8.4)
	Blood creatinine increased*	17 (6.2)	2 (0.7)
	Blood alkaline phosphatase increased	20 (7.3)	2 (0.7)
	Amylase increased	9 (3.3)	4 (1.5)
	Lipase increased	14 (5.1)	7 (2.6)

*composite terms which included more than one preferred term

[a] includes keratoacanthoma, squamous cell carcinoma, lip squamous cell carcinoma and squamous cell carcinoma of skin

[b] includes angioedema, drug hypersensitivity, hypersensitivity, hypersensitivity vasculitis and urticaria

[c] includes facial nerve disorder, facial paralysis, facial paresis

[d] includes left ventricular dysfunction, ejection fraction decreased, cardiac failure and ejection fraction abnormal

[e] includes haemorrhage at various sites including cerebral haemorrhage
[f] includes pulmonary embolism, deep vein thrombosis, embolism, thrombophlebitis, thrombophlebitis superficial and thrombosis
[g] includes colitis, colitis ulcerative, enterocolitis and proctitis
[h] includes myalgia, muscular weakness, muscle spasm, muscle injury, myopathy, myositis
[i] includes fluid retention, peripheral oedema, localised oedema

Severity of Adverse Events

Bini P vs Combo 450 RP (pooled sets)

In the Bini P population, the maximum reported severity of AEs was Grade 1, 2, 3 and 4 for 6.1%, 27.2%, 53.6% and 13.1% of patients, respectively.

In the Combo 450 RP population, the maximum reported severity of AEs was Grade 1, 2, 3 and 4 for 10.2%, 30.7%, 48.2% and 9.9% of patients, respectively, indicating less Grade 3 AEs (5.4% difference) than in the Bini P population.

When encorafenib was used at a dose of 300 mg once daily in combination with binimetinib 45 mg twice daily (Combo 300) in study CMEK162B2301-Part 2, the frequency category was lower compared to the pooled Combo 450 population for the following adverse reactions: anemia, peripheral neuropathy, haemorrhage, hypertension, pruritus (common) and colitis, increased amylase and increased lipase (uncommon).

Adverse Events by Time of Onset

Bini P vs Combo 450 RP (pooled sets).

The median time to onset of first Grade 3/4 AEs was longer in the Combo 450 RP population than the Bini P population: 2.6 months (95% CI: 1.8, 3.2) vs 1.0 month (95% CI: 0.9, 1.3).

Of note, a shorter time to onset was reported for the Combo BP population (1.8 months; 95% CI: 1.4, 2.4) than the Combo 450 RP population.

Adverse events of special interest (AESI)

These were identified based on the known class effects of MEK- and BRAF- inhibitors as well as emerging safety signals from the clinical program and health authority interactions. Table 70 and Table 71 present an overview of AESIs by category (AESIs related to both drugs, specifically to encorafenib and specifically to binimetinib) and grouping (overall and Grade 3/4) for patients in the three treatment arms of Study CMEK162B2301 and also includes separate columns for patients from the Bini 45mg BID, Enco 300mg QD and the Combo 450 RP pooled doses population.

Table 70: Adverse of special interest - regardless of relationship to study drug – overall and maximum Grades 3 and 4 – AESIs relating to both drugs

	Melanoma				Study CMEK162B2301		
	Binimetinib 45 mg BID N=427	Encorafenib 300 mg QD N=217	Combo pooled doses N=433	Combo 450 mg QD N=274	Combo 450 mg QD N=192	Encorafenib 300 mg QD N=192	Vemurafenib N=186
Grouping	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
AESIs Relating to Both Binimetinib and Encorafenib							
Retinopathy excluding RVO	189 (44.3)	27 (12.4)	232 (53.6)	144 (52.6)	93 (48.4)	26 (13.5)	23 (12.4)
Grade 3/4	9 (2.1)	0	11 (2.5)	6 (2.2)	5 (2.6)	0	0
Rash	353 (82.7)	111 (51.2)	104 (24.0)	65 (23.7)	50 (26.0)	95 (49.5)	111 (59.7)
Grade 3/4	29 (6.8)	12 (5.5)	3 (0.7)	2 (0.7)	2 (1.0)	10 (5.2)	25 (13.4)
Liver function test abnormalities	74 (17.3)	30 (13.8)	107 (24.7)	69 (25.2)	48 (25.0)	28 (14.6)	39 (21.0)
Grade 3/4	18 (4.2)	12 (5.5)	50 (11.5)	34 (12.4)	28 (14.6)	11 (5.7)	7 (3.8)
Muscle enzyme/protein changes	191 (44.7)	3 (1.4)	94 (21.7)	68 (24.8)	44 (22.9)	3 (1.6)	4 (2.2)
Grade 3/4	89 (20.8)	0	22 (5.1)	15 (5.5)	13 (6.8)	0	0
Myopathy	66 (15.5)	73 (33.6)	69 (15.9)	44 (16.1)	32 (16.7)	60 (31.3)	37 (19.9)
Grade 3/4	10 (2.3)	20 (9.2)	2 (0.5)	2 (0.7)	0	19 (9.9)	1 (0.5)
Skin infections	74 (17.3)	24 (11.1)	41 (9.5)	31 (11.3)	22 (11.5)	23 (12.0)	26 (14.0)
Grade 3/4	20 (4.7)	1 (0.5)	7 (1.6)	4 (1.5)	4 (2.1)	1 (0.5)	0
PPE syndrome	5 (1.2)	112 (51.6)	19 (4.4)	16 (5.8)	13 (6.8)	98 (51.0)	26 (14.0)
Grade 3/4	1 (0.2)	27 (12.4)	0	0	0	26 (13.5)	2 (1.1)
Photosensitivity	7 (1.6)	9 (4.1)	15 (3.5)	10 (3.6)	9 (4.7)	9 (4.7)	70 (37.6)
Grade 3/4	0	0	1 (0.2)	1 (0.4)	1 (0.5)	0	3 (1.6)
Uveitis type events	1 (0.2)	1 (0.5)	16 (3.7)	8 (2.9)	7 (3.6)	1 (0.5)	7 (3.8)
Grade 3/4	0	0	2 (0.5)	1 (0.4)	1 (0.5)	0	0
Nail disorders	19 (4.4)	6 (2.8)	6 (1.4)	5 (1.8)	3 (1.6)	6 (3.1)	0
Grade 3/4	1 (0.2)	0	0	0	0	0	0
Severe cutaneous adverse reactions	5 (1.2)	3 (1.4)	2 (0.5)	2 (0.7)	1 (0.5)	2 (1.0)	8 (4.3)
Grade 3/4	0	1 (0.5)	0	0	0	1 (0.5)	5 (2.7)
Hepatic failure	1 (0.2)	0	1 (0.2)	1 (0.4)	1 (0.5)	0	0
Grade 3/4	1 (0.2)	0	1 (0.2)	1 (0.4)	1 (0.5)	0	0
Rhabdomyolysis	2 (0.5)	0	1 (0.2)	1 (0.4)	1 (0.5)	0	0
Grade 3/4	2 (0.5)	0	1 (0.2)	1 (0.4)	1 (0.5)	0	0
Retinal vein occlusion	9 (2.1)	0	0	0	0	0	0
Grade 3/4	5 (1.2)	0	0	0	0	0	0

Table 71: Adverse of special interest - regardless of relationship to study drug – overall and maximum Grades 3 and 4 – AESIs relating to Binimetinib / Encorafenib alone

	Melanoma		Study CMEK162B2301				
	Binimetinib 45 mg BID N=427	Encorafenib 300 mg QD N=217	Combo pooled doses N=433	Combo 450 mg N=274	Combo 450 mg QD N=192	Encorafenib 300 mg QD N=192	Vemurafenib N=186
Grouping	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
AESIs Relating to Binimetinib Alone							
Haemorrhage	49 (11.5)	28 (12.9)	69 (15.9)	43 (15.7)	35 (18.2)	24 (12.5)	15 (8.1)
Grade 3/4	10 (2.3)	4 (1.8)	15 (3.5)	7 (2.6)	6 (3.1)	4 (2.1)	3 (1.6)
Peripheral oedema	202 (47.3)	24 (11.1)	65 (15.0)	40 (14.6)	24 (12.5)	19 (9.9)	22 (11.8)
Grade 3/4	4 (0.9)	0	2 (0.5)	2 (0.7)	2 (1.0)	0	2 (1.1)
Hypertension	68 (15.9)	12 (5.5)	45 (10.4)	33 (12.0)	22 (11.5)	12 (6.3)	21 (11.3)
Grade 3/4	37 (8.7)	6 (2.8)	19 (4.4)	17 (6.2)	11 (5.7)	6 (3.1)	6 (3.2)
Left ventricular dysfunction	48 (11.2)	4 (1.8)	31 (7.2)	23 (8.4)	15 (7.8)	4 (2.1)	2 (1.1)
Grade 3/4	18 (4.2)	2 (0.9)	4 (0.9)	3 (1.1)	3 (1.6)	2 (1.0)	0
Venous thromboembolism	17 (4.0)	6 (2.8)	14 (3.2)	11 (4.0)	10 (5.2)	6 (3.1)	3 (1.6)
Grade 3/4	6 (1.4)	2 (0.9)	5 (1.2)	2 (0.7)	2 (1.0)	2 (1.0)	1 (0.5)
Bradycardia	13 (3.0)	1 (0.5)	5 (1.2)	4 (1.5)	2 (1.0)	1 (0.5)	2 (1.1)
Grade 3/4	0	0	0	0	0	0	1 (0.5)
Pneumonitis	6 (1.4)	2 (0.9)	1 (0.2)	1 (0.4)	1 (0.5)	2 (1.0)	1 (0.5)
Grade 3/4	2 (0.5)	0	0	0	0	0	1 (0.5)
AESIs Relating to Encorafenib Alone							
Acute renal failure	8 (1.9)	6 (2.8)	15 (3.5)	8 (2.9)	7 (3.6)	5 (2.6)	9 (4.8)
Grade 3/4	2 (0.5)	3 (1.4)	9 (2.1)	5 (1.8)	5 (2.6)	3 (1.6)	3 (1.6)
Cutaneous squamous cell carcinoma	1 (0.2)	15 (6.9)	8 (1.8)	7 (2.6)	5 (2.6)	15 (7.8)	31 (16.7)
Grade 3/4	1 (0.2)	0	0	0	0	0	12 (6.5)
Cutaneous non-squamous cell carcinoma	3 (0.7)	2 (0.9)	10 (2.3)	5 (1.8)	4 (2.1)	2 (1.0)	5 (2.7)
Grade 3/4	0	1 (0.5)	0	0	0	1 (0.5)	1 (0.5)
Tachycardia	17 (4.0)	13 (6.0)	7 (1.6)	5 (1.8)	3 (1.6)	12 (6.3)	10 (5.4)
Grade 3/4	5 (1.2)	3 (1.4)	2 (0.5)	1 (0.4)	1 (0.5)	2 (1.0)	1 (0.5)
Facial paresis	0	16 (7.4)	3 (0.7)	2 (0.7)	2 (1.0)	14 (7.3)	1 (0.5)
Grade 3/4	0	3 (1.4)	1 (0.2)	1 (0.4)	1 (0.5)	3 (1.6)	0
Melanomas	0	10 (4.6)	0	0	0	10 (5.2)	8 (4.3)
Grade 3/4	0	3 (1.4)	0	0	0	3 (1.6)	6 (3.2)

Retinal events

Retinal events were reported in a higher incidence in the Combo 450 RP population compared to the Bini P population but this tendency was reversed when considering adjustment for study drug exposure. However, regarding the PTs, retinal detachment was reported at a higher incidence for the binimetinib monotherapy (10.3% Bini P vs 6.6% Combo 450), vision blurred for the combination therapy (15.3% Combo 450 vs 6.6% Bini P). In summary, an additive adverse effect of binimetinib and encorafenib regarding Retinopathy can be suggested. Grade 3 events occurred not very frequent and most of the events were transient, self-limiting and reversible and the proposed recommendations regarding management and dose modification seem to be acceptable. However, it should be kept in mind that events under the PT of blindness (in the grouping of retinopathy excluding RVO) were reported in 3 patients in Study CMEK162B2301 Part 1 (2 patients in the Combo 450 arm

[CMEK162B2301 Patient 4015- 015 and CMEK162B2301 Patient 6085-003] and 1 patient in the encorafenib 300mg monotherapy Part 1 arm [CMEK162B2301 Patient 6085-005]). In the Bini P population, no cases of blindness were reported.

Vascular eye events (RVO) as potentially sight–threatening events were seen only in the Bini P population (2.1%). In contrast uveitis-Type AESIs were mainly reported for the Combo 450 RP population but only in a quite low incidence and in a mild severity 2.9%).

Ocular events

In the pooled Combo 450 population, RPED was reported in 29.6 % (81/274) of patients. RPED was Grade 1 (asymptomatic) in 21.2 % (58/274) of patients, Grade 2 in 6.6 % (18/274) of patients and Grade 3 in 1.8 % (5/274) of patients. Most events were reported as retinopathy, retinal detachment, subretinal fluid, macular oedema, and chorioretinopathy and led to dose interruptions or dose modifications in 4.7 % (13/274) of patients. The median time to onset of the first event of RPED (all grades) was 1.5 month (range 0.03 to 17.5 months).

Visual impairment, including vision blurred and reduced visual acuity, occurred in 21.5 % (59/274) of patients. Visual impairment was generally reversible.

Uveitis was also reported when binimetinib was used in combination with encorafenib (see section 4.8 of encorafenib SmPC).

In Study CMEK162B2301-Part 2, in the Combo 300 arm, RPED was observed in 12.5% (32/257) of patients with 0.4% (1/257) Grade 4 event.

Dermatologic reactions

Dermatologic reactions may occur when binimetinib is used in combination with encorafenib.

Rash is among the most frequently observed AEs reported for both monotherapy populations (Bini P 82.7%, Enco P 51.2%) and is reported at a remarkably lower frequency when binimetinib and encorafenib are combined (Combo 450 RP 23.7%). Compared to other MEK/BRAF inhibitor combinations the incidence of rash seems to be lower for the combination therapy with binimetinib and encorafenib. In addition, it should be kept in mind that, with regard to the preliminary data of part 2 of the pivotal study, the incidence of rash seems to be lower in the Combo 300 mg population (7.0% vs 14.1%). In the pooled Combo 450 population, rash occurred in 19.7 % (54/274) of patients. Most events were mild, with Grade 3 or 4 events reported in 0.7 % (2/274) of patients. Rash led to treatment discontinuation in 0.4 % (1/274) of patients and to dose interruption or dose modification in 1.1 % (3/274) of patients.

In patients treated with Combo 450, dermatitis acneiform occurred in 4.4 % (12/274) of patients, was Grade 1 and 2 and no event led to treatment discontinuation. Dose modification was reported in 0.7 % (2/274) of patients.

In contrast, palmar-plantar Erythrodysaesthesia (PPES) is reported in a remarkably higher incidence for the encorafenib monotherapy (Enco P 51.6%) compared to the Bini P (1.2%) and Combo 450 RP (5.8%) populations. However, according to the presented data of part 2 of the pivotal study, the incidence of PPE is higher with the lower dose of encorafenib (Combo 300). PPES can occur when binimetinib is used in combination with encorafenib. Please refer to the encorafenib SmPC.

Photosensitivity reaction occurred in 4.7% of the patients in the Combo 450 arm in the pivotal study and was identified also as a relevant toxicity of binimetinib (and encorafenib) in the non-clinical trials. In the pooled Combo 450 population, photosensitivity was observed in 4.0 % (11/274) of patients. Most events were Grade 1-2, with Grade 3 reported in 0.4 % (1/274) of patients and no event led to discontinuation. Dose interruption or dose modification was reported in 0.4 % (1/274) of patients.

The incidence of skin infections was remarkably lower in the Combo 450 RP population than in the Binimetinib monotherapy set (11.3%-1.10 cases per 100 patient-months vs 17.3%-4.60 cases per 100 patient-months).

Liver function test abnormalities AESIs were reported at a remarkably higher incidence in the Combo 450 RP population than in the Bini P population, overall (25.2% vs 17.3%), for Grade 3/4 AESIs (12.4% vs 4.2%) and for AESIs requiring dose adjustment/study drug interruption (8.4% vs 3%). Regarding the PTs, GGT increased was reported at a higher incidence for the encorafenib monotherapy and the combination therapy population than for the binimetinib monotherapy population (Enco P 10.6%, Combo 450 RP 13.9 % vs Bini P 3.5%). In contrast ALT/AST increased was reported in a higher incidence for the binimetinib monotherapy and the combination therapy population than for the encorafenib monotherapy population.

Liver laboratory abnormalities

The incidences of liver laboratory abnormalities reported in the pooled Combo 450 population are listed below:

- Increased transaminases: 15.7% (43/274) overall – Grade 3-4: 5.5% (15/274)
- Increased GGT: 14.6% (40/274) overall – Grade 3-4: 8.4% (23/274)

In Study CMEK162B2301-Part 2, in the Combo 300 arm, the incidences of liver laboratory abnormalities are listed below:

- Increased transaminases: 13.2% (34/257) overall – Grade 3-4: 5.4% (14/257)
- Increased GGT: 14.0% (36/257) overall – Grade 3-4: 4.7% (12/257)

Elevation of blood CK

Elevation of blood CK is a frequently observed laboratory finding associated with the administration of Binimetinib 45 mg monotherapy and is clinically associated sometimes with concomitant muscular symptoms. However, the addition of encorafenib to binimetinib appears to mitigate this effect as demonstrated by fewer patients in the Combo 450 RP population experiencing CK elevations as compared with the Bini P population (24.8%-2.66 cases per 100 patient-months vs 44.7%-18.86 cases per 100 patient-months), as well as a lower incidence of Grade 3/4 events, SAEs, AEs leading to discontinuation, AEs requiring dose interruption and/or change and AEs requiring additional therapy.

In the pooled Combo 450 population, mostly mild asymptomatic blood CK elevation was reported in 27.0 % (74/274) of patients. The incidence of Grade 3 or 4 adverse reactions was 5.8 % (16/274). The median time to onset of the first event was 2.7 months (range: 0.5 to 17.5 months).

Rhabdomyolysis was reported in 0.4 % (1/274) of patients treated with encorafenib in combination with binimetinib. In this patient, rhabdomyolysis was observed with concomitant symptomatic Grade 4 CK elevation.

In contrast, muscle-related AEs, including myalgia, is a frequently observed with the administration of Encorafenib 300 mg monotherapy. However, the combination of binimetinib and encorafenib appears to mitigate this effect as demonstrated by fewer patients in the Combo 450 arm experiencing muscle-related AEs as compared with the encorafenib 300 mg monotherapy arm Part 1 (16.7% vs 31.3%), as well as a distinctly lower incidence of Grade 3/4 events, SAEs, AEs leading to discontinuation, AEs requiring dose interruption and/or change and AEs requiring additional therapy.

The incidence of cardiac events (a significant safety concern of Binimetinib monotherapy) was similar respectively lower after adjustment for treatment exposure in the Combo 450 RP population compared

to the Bini P population (8.4%-0.79 case per 100 patient-months vs 11.2%-2.77 cases per 100 patient-months). Grade 3/4 events were reported at a remarkably lower incidence in the Combo 450 RP population than in the Bini P population (1.1% vs 4.2%). In addition, there were no events leading to study drug discontinuation in the Combo 450 RP population whilst 4.2% were reported in the Bini P population. Few events were serious or required additional therapy. The most frequent PT in both populations was ejection fraction decreased (Combo 450 RP 6.6% vs Bini P 10.3%).

Overall, regarding the presented data of part 2 of the pivotal study CMEK162B2301 the frequency of patients with events in the left ventricular dysfunction grouping in the Combo 450 arm (7.8% [1.6% Grade 3/4]) seems to be similar to that in the Combo 300 arm (5.8% [1.2% Grade 3/4], showing equivalent tolerability between these 2 Combo dose arms and with no increased burden to patients with the higher encorafenib dose in the Combo 450 arm.

Cardiac electrophysiology

In the safety analysis of pooled studies of encorafenib 450 mg once daily in combination with 45 mg binimetinib twice daily (Combo 450), the incidence of new QTc prolongation > 500 ms was 0.7 % (2/268) in the encorafenib 450 mg plus binimetinib group, and 2.5 % (5/203) in the encorafenib single agent group. QTc prolongation of > 60 ms compared to pre-treatment values was observed in 4.9 % (13/268) patients in the encorafenib plus binimetinib group, and in 3.4 % (7/204) in the encorafenib single agent group (see section 5.1 of encorafenib SmPC).

Left ventricular dysfunction

In the pooled Combo 450 population, LVD was reported in 8.4 % (23/274) of patients. Grade 3 events occurred in 1.1 % (3/274) of patients. LVD led to treatment discontinuation in 0.4% (1/274) of patients and led to dose interruptions or dose reductions in 6.6 % (18/274) of patients.

The median time to first occurrence of LVD (any grade) was 4.4 months (range 0.03 to 21.3 months) in patients who developed an LVEF below 50 %. The mean LVEF value dropped by 5.9 % in the pooled Combo 450 population, from a mean of 63.9 % at baseline to 58.1 %. LVD was generally reversible following dose reduction or dose interruption.

Venous thromboembolism

In patients treated with Combo 450, VTE occurred in 4.7 % (13/274) of patients, including 2.2 % (6/274) of patients who developed pulmonary embolism. In the pooled Combo 450 population, VTE was reported as Grade 1 or 2 in 3.6 % (10/274) of patients and Grade 3 or 4 in 1.1 % (3/274) of patients. VTE led to dose interruptions or dose modifications in 1.1 % (3/274) patients and to additional therapy in 4.7 % (13/274) of patients.

Hypertension

Hypertension AESIs were reported at a similar incidence in the Bini P and Combo 450 RP populations overall, although the incidence was higher in the Bini P when adjusted for drug exposure (15.9%-4.49 cases per 100 patient-months vs 12%-1.19 cases per 100 patient-months) and for Grade 3/4 events (8.7% vs 6.2%).

In Study CMEK162B2301 the incidence of a 2-grade shift in LVEF was higher in in the hypertension risk factor group (=history of hypertension, SBP ≥140 at screening, or DBP ≥ 90 at screening) as well. Thus, severe hypertension should be controlled before initiating treatment with binimetinib.

The incidence of hypertension AESIs was similar in the Combo 450 and vemurafenib arms of the pivotal study, overall (11.5%-1.01 cases per 100 patient-months vs 11.3%-1.49 cases per 100 patient-months) and for Grade 3/4 events (5.7% vs 3.2%).

New onset elevated blood pressure or worsening of pre-existing hypertension were reported in 11.7 % (32/274) of patients treated with the Combo 450. Hypertension events were reported as Grade 3 in 5.5 % (15/274) of patients, including hypertensive crisis (0.4 % (1/274)). Hypertension led to dose interruption or adjustment in 2.9 % of patients. Hypertensive adverse reactions required additional therapy in 8.0 % (22/274) of patients.

Haemorrhage

Haemorrhage AESIs were reported at a similar overall incidence in the Bini P, Enco P and Combo 450 RP populations (11.5%-2.98 cases per 100 patient-months vs 12.9%-1.52 cases per 100 patient-month vs 15.7%-1.55 cases per 100 patient months). Additionally, with regard to the preliminary data of part 2 of the pivotal study the incidence of haemorrhage events seems to be lower in the Combo 300mg population compared to the Combo 450 mg arm (7.0% vs 18.2%).

Haemorrhagic events were observed in 17.9 % (49/274) of patients in the pooled Combo 450 population. Most of these cases were Grade 1 or 2 (14.6 %) and 3.3 % were Grade 3 or 4 events. Few patients requiring dose interruptions or dose reductions (0.7 % or 2/274). Haemorrhagic events led to discontinuation of treatment in 1.1 % (3/274) of patients. The most frequent haemorrhagic events were haematuria in 3.3 % (9/274) of patients, rectal haemorrhage in 2.9 % (8/274) and haematochezia in 2.9 % (8/274) of patients. Fatal gastric ulcer haemorrhage with multiple organ failure as a concurrent cause of death, occurred in one patient. Cerebral haemorrhage occurred in 1.5 % (4/274) of patients with fatal outcome in 3 patients. All events occurred in the setting of new or progressive brain metastases.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, haemorrhagic events were observed in 6.6% (17/257) of patients and were Grade 3-4 in 1.6% (4/257) of patients.

Anaemia

In the pooled Combo 450 population, anaemia was reported in 19.7 % (54/274) of patients; 4.7 % (13/274) of patients had Grade 3 or 4. No patients discontinued treatment due to anaemia, 1.5 % (4/274) required dose interruption or dose modification.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, anaemia was observed in 9.7% (25/257) of patients with Grade 3-4 reported in 2.7% (7/257) patients.

Bradycardia and peripheral oedema

Bradycardia and peripheral oedema have been identified as AESIs for binimetinib. However, the incidences of these AESIs are remarkably reduced when binimetinib is given in combination with encorafenib.

Pneumonitis

AESIs were reported at a similar (low) overall incidence in the Bini P and Combo 450 RP populations.

Facial paresis

Facial paresis was reported when binimetinib was used in combination with encorafenib (see section 4.8 of encorafenib SmPC).

Increased heart rate and facial paresis have been identified as an AESI for encorafenib. However, the incidence of these AESIs is remarkably reduced when encorafenib is given in combination with binimetinib.

Renal dysfunction

Blood creatinine elevation and renal failure occurred when binimetinib was used in combination with encorafenib (see section 4.8 of encorafenib SmPC).

The incidence of renal failures seems to be similar in the presented safety populations. However, the severity seems to be slightly higher in the combo 450 RP population than in the binimetinib and encorafenib mono populations (incidence of Grade ¾ events: Bini P 0.5%, Enco P 1.4%, Combo 450 1.8%). However, laboratory serum creatinine elevations were reported in most of the patients in the Combo 450 arm of the pivotal study (overall 92. 7%). Although most of the creatinine elevations seem to be asymptomatic, the grade ¾ elevations seem to result in renal failures.

Cutaneous malignancies

Secondary skin neoplasms have been identified as an AESI for encorafenib. Regarding the data presented (CMEK162B2301) the addition of binimetinib to encorafenib appears to attenuate the development of cutaneous squamous cell carcinoma (cuSCC) as compared to encorafenib treatment alone (Combo 450 arm2.6% vs enco 300 arm 7.8%).

Compared to vemurafenib cuSCC AESIs were reported at a distinctly lower incidence in the Combo 450 arm (2.6%) than the vemurafenib arm (16.7%), overall, for Grade 3/4 events (none vs 6.5%) and for events requiring additional therapy (1% vs 12.4%). However, compared to the combination vemurafenib / cobimetinib the incidences seem to be similar.

Cutaneous non-squamous cell carcinoma (cuSCC) events were reported in a low percentage of patients overall (2.1% Combo 450 arm, 1.0% encorafenib 300 arm, 2.7% vemurafenib arm). No melanoma events were reported for any patient in the Combo 450 arm while in the encorafenib 300 arm and vemurafenib arm, melanoma events occurred in a similar percentage of patients (5.2% encorafenib Part 1 arm, 4.3% vemurafenib arm). CuSCC was reported when binimetinib was used in combination with encorafenib (see section 4.8 of encorafenib SmPC).

Compared to the combination dabrafenib/trametinib the incidence of pyrexia in the Combo 450 mg RP seem to be distinctly lower (53% vs 15.7%) and other secondary causes were generally evident. However, it should be kept in mind that the most commonly reported SAE by PT in the Combo 450 arm of Study CMEK162B2301 Part 1 was pyrexia in 6 (3.1%) patients. None of the 6 patients had concurrent events of hypotension, chills/rigors, dehydration, renal failure or syncope and most of the patients had concurrent factors including disease progression or underlying infection which may have contributed to the pyrexia.

Pancreatitis

The pancreatic enzyme elevations in the combo 450 RP population (Lipase 4.7%, Amylase 2.9%) were mostly asymptomatic. Pancreatitis is an uncommon ADR (incidence <1%) when encorafenib is used in combination with binimetinib. Pancreatitis was reported when binimetinib was used in combination with encorafenib (see section 4.8 of encorafenib SmPC).

Gastrointestinal disorders

In the pooled Combo 450 population, diarrhoea was observed in 38 % (104/274) of patients and was Grade 3 or 4 in 3.3 % (9/274) of patients. Diarrhoea led to dose discontinuation in 0.4 % of patients and to dose interruption or dose modification in 4.4 % of patients. Constipation occurred in 24.1 % (66/274) of patients and was Grade 1 or 2. Abdominal pain was reported in 27.4 % (75/274) of patients and was Grade 3 in 2.6 % (7/274) patients. Nausea occurred in 41.6 % (114/274) with Grade 3 or 4 observed in 2.6 % (7/274) of patients. Vomiting occurred in 28.1 % (77/274) of patients with Grade 3 or 4 reported in 2.2 % (6/274) of patients.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, nausea was observed in 27.2% (70/257) of patients and was Grade 3 in 1.6% (4/257) of patients. Vomiting occurred in 15.2% (39/257) of patients with Grade 3 reported in 0.4% (1/257) of patients. Diarrhoea occurred in 28.4% (73/257) of patients with Grade 3 reported in 1.6% (4/257) of patients.

Gastrointestinal disorders were typically managed with standard therapy.

Headache
In the pooled Combo 450 population, headache occurred in 21.5% (59/274) of patients including Grade 3 in 1.5% (4/274) of patients.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, headache was reported in 12.1% (31/257) of patients and was Grade 3 in 0.4% (1/257) of patients.

Fatigue
In the pooled Combo 450 population, fatigue occurred in 43.8% (120/274) of patients including Grade 3 in 2.9% (8/274) of patients.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, fatigue was observed in 33.5% (86/257) of patients with 1.6% (4/257) Grade 3-4 events.

Combo BP versus Combo 450 RP:

The overall safety profile (as of 09 November 2016 data cutoff) of overall AEs, SAEs and AEs leading to treatment discontinuation is similar between Combo BP and Combo 450 RP populations. Discrete AE PTs reported in the Combo BP but not in Combo 450 RP occurred at an incidence of <1%, were non-specific, and no new safety concerns were identified from the Combo BP.

Serious adverse event / deaths / other significant events

Deaths

On-treatment deaths for all studies included in the Broad Safety Set were collected while patients were on treatment or within 30 days of the last dose of study drug.

Table 65 presents a summary of on-treatment deaths (occurring during treatment or within 30 days of the last dose) by PT for the Broad Safety Set.

Bini P vs Combo 450 RP (pooled sets)

The overall incidence of on-treatment deaths (with or without adjustment for study drug exposure) was lower in the Combo 450 RP population compared to the Bini P population (8.4% vs 10.8%), with EAIR of deaths per 100 patient-months of 0.74 vs 2.45 and with most deaths in both populations due to progression of malignant melanoma (5.8% Combo 450 vs 9.4% Bini P).

The higher incidence of deaths not related to progression in the Combo 450 RP population is due to the higher exposure duration to Combo 450 than to binimetinib alone.

Overall two deaths due to AE (sepsis and multiorgan failure) and 10 deaths due to disease progression occurred within 30 days of the first dose of study drug in the Bini P population and a single death (due to AE: completed suicide) occurred within 30 days of the first dose of study drug in the Combo 450 RP population (Combo 450 arm of study CMEK162B2301).

Combo 450 vs vemurafenib (Study CMEK162B2301)

The overall incidence of on-treatment deaths (with or without adjustment for study drug exposure) was slightly lower in the Combo 450 arm (8.9%, with an EAIR of deaths per 100 patient-months of

0.71) than the vemurafenib arm (10.2%, with an EAIR of deaths per 100 patient-months of 1.23), with most deaths in both arms due to progression of malignant melanoma (5.2% vs 9.1%).

In the Combo 450 arm, one death (completed suicide) occurred within 30 days of the first dose of study drug vs no deaths in the vemurafenib arm.

Table 72: On-treatment Deaths by Primary System Organ Class, Preferred Term and Treatment (Broad Safety Set)

	Melanoma				Study CMEK162B2301		
Principal cause of death	Bini 45mg BID N=427 n (%)	Enco 300mg QD N=217 n (%)	Combo pooled doses N=433 n (%)	Combo 450mg QD N=274 n (%)	Combo 450mg QD N=192 n (%)	Enco 300mg QD N=192 n (%)	Vemurafenib N=186 n (%)
Any primary system organ class	46 (10.8)	15 (6.9)	44 (10.2)	23 (8.4)	17 (8.9)	14 (7.3)	19 (10.2)
Malignant melanoma	40 (9.4)	12 (5.5)	28 (6.5)	16 (5.8)	10 (5.2)	12 (6.3)	17 (9.1)
Death	0	1 (0.5)	3 (0.7)	2 (0.7)	2 (1.0)	1 (0.5)	0
Cerebral haemorrhage	0	0	1 (0.2)	1 (0.4)	1 (0.5)	0	0
Completed suicide	0	0	1 (0.2)	1 (0.4)	1 (0.5)	0	0
Euthanasia	1 (0.2)	0	1 (0.2)	1 (0.4)	1 (0.5)	0	0
Metastases to central nervous system	0	0	1 (0.2)	1 (0.4)	1 (0.5)	0	0
Multiple organ dysfunction syndrome	0	0	1 (0.2)	1 (0.4)	1 (0.5)	0	0
Acute myocardial infarction	0	1 (0.5)	0	0	0	1 (0.5)	0
Disease progression	0	0	1 (0.2)	0	0	0	0
Dyspnoea	1 (0.2)	0	0	0	0	0	0
Embolism	1 (0.2)	0	0	0	0	0	0
Intestinal sepsis	0	0	0	0	0	0	1 (0.5)
Lung infection	0	0	0	0	0	0	1 (0.5)
Malignant melanoma stage IV	0	0	1 (0.2)	0	0	0	0
Metastatic malignant melanoma	0	0	4 (0.9)	0	0	0	0
Multi-organ failure	1 (0.2)	0	0	0	0	0	0
Myocardial infarction	0	0	1 (0.2)	0	0	0	0
Neoplasm progression	0	0	1 (0.2)	0	0	0	0
Sepsis	2 (0.5)	0	0	0	0	0	0

Source: ISS Table 2.7.1
Preferred terms are sorted in descending frequency in the 'Combo 450 mg QD-melanoma' column
MedDRA Version 19.0 has been used for the reporting of adverse events.

Deaths related to adverse events in patients treated with binimetinib monotherapy

In the 2 studies that provide safety results for patients receiving binimetinib 45 mg monotherapy (Studies CMEK162A2301 and CMEK162X2201, a total of 6 patients died due to events other than disease progression (Table 73).

Table 73: On-Treatment Deaths Considered Due to an Adverse Event (Binimetinib 45 mg)

Patient ID	Age	Gender	Cause of death by PT	Study day of last dose	Study day of death
Study CMEK162A2301					
3015-016	65	M	sepsis	80	88
4011-006	64	M	sepsis	15	16
3012-005	78	M	multiple organ failure	22	23
6051-004	52	F	embolism	153	171
Study CMEK162X2201					
1201-00101	47	F	euthanasia	116	132
1101-00101	58	F	dyspnoea	96	96

Source: CMEK162A2301 and CMEK162X2201 CSRs.
Abbreviations: F = female; ID = identification number; M = male; PT = preferred term.

Deaths related to adverse events in patients treated with Combo (450-600 mg)

In the Broad Safety Set, a total of 7 patients receiving Combo 450 mg or 600 mg died due to events other than disease progression (malignant melanoma/metastases), including 6 patients in Study CMEK162B2301 and 1 patient in Study CMEK162X2110. A summary of on-treatment deaths considered due to an AE is provided in Table 74.

Table 74: On-Treatment Deaths Considered Due to an Adverse Event (Combo 450 mg or 600 mg)

Patient ID	Age	Gender	Cause of death by PT	Study day of last dose	Study day of death
Study CMEK162B2301					
2056-004	51	F	death	148	148
4075-011	35	M	death	77	77
3010-010	67	M	multiple organ dysfunction syndrome	15	37
4023-002	54	M	cerebral haemorrhage	230	246
8010-001	73	F	completed suicide	9	24
8045-011	43	M	euthanasia	256	268
Study CMEK162X2110					
2000-210[b]	65	M	myocardial infarction	160	160

Source: CMEK162B2301, CLGX818X2109 and CMEK162X2110 CSRs.

F: female, ID: identification number, M: male, PT: preferred term

[a]All deaths in this study were more than 30 days after the last dose of Combo 450 mg.

[b]Patient received encorafenib at a dose of 600 mg QD in combination with binimetinib 45 mg BID.

Deaths in the Other On-going Studies

Of the 30 patients treated in Compassionate Use Protocols and Investigator-sponsored trials with single-agent binimetinib, single-agent encorafenib or the combination of encorafenib plus binimetinib in the relevant *NRAS*/*BRAF*-mutant metastatic melanoma population, 11 patients (all treated with binimetinib) had SAEs with a fatal outcome. Of these 11 patients, 6 fatal outcomes were due to PD, 1 was due to an SAE of pneumonia (only PT reported as related to the study drug by the Investigator) and sepsis, 1 was due to an SAE of ileus and multi-organ failure and 3 others provided no further information other than patient death. The SAE of pneumonia was the only reported as related with the study drug.

Serious Adverse Events in Completed Studies

SAEs in the Broad Safety Set

A summary of SAEs, regardless of relationship to study drug, that were reported for ≥2% of patients in any population by PT (overall and Grade 3/4 maximum) for the Broad Safety Set are presented in Table 75.

Table 75: Serious Adverse Events, Regardless of Study Drug Relationship, by Preferred Term and Treatment - Overall and Maximum Grade 3 or 4 (≥2% in any population) (Broad Safety Set)

	Melanoma				Study CMEK162B2301		
Preferred Term Grades	Bini 45mg BID N=427 n (%)	Enco 300mg QD N=217 n (%)	Combo pooled doses N=433 n (%)	Combo 450mg QD N=274 n (%)	Combo 450mg QD N=192 n (%)	Enco 300mg QD N=192 n (%)	Vemurafenib N=186 n (%)
Any preferred term							
All grades	141 (33.0)	69 (31.8)	158 (36.5)	98 (35.8)	66 (34.4)	65 (33.9)	69 (37.1)
Grades 3/4	116 (27.2)	58 (26.7)	142 (32.8)	87 (31.8)	57 (29.7)	54 (28.1)	60 (32.3)
Pyrexia							
All grades	0	3 (1.4)	15 (3.5)	6 (2.2)	6 (3.1)	3 (1.6)	2 (1.1)
Grades 3/4	0	2 (0.9)	9 (2.1)	5 (1.8)	5 (2.6)	2 (1.0)	0
Pneumonia							
All grades	2 (0.5)	1 (0.5)	7 (1.6)	6 (2.2)	3 (1.6)	0	0
Grades 3/4	2 (0.5)	1 (0.5)	4 (0.9)	4 (1.5)	3 (1.6)	0	0
Nausea							
All grades	3 (0.7)	6 (2.8)	15 (3.5)	6 (2.2)	2 (1.0)	6 (3.1)	0
Grades 3/4	2 (0.5)	4 (1.8)	11 (2.5)	5 (1.8)	1 (0.5)	4 (2.1)	0
Anaemia							
All grades	3 (0.7)	1 (0.5)	8 (1.8)	5 (1.8)	4 (2.1)	1 (0.5)	2 (1.1)
Grades 3/4	3 (0.7)	1 (0.5)	8 (1.8)	5 (1.8)	4 (2.1)	1 (0.5)	1 (0.5)
Vomiting							
All grades	5 (1.2)	6 (2.8)	17 (3.9)	5 (1.8)	3 (1.6)	6 (3.1)	2 (1.1)
Grades 3/4	4 (0.9)	6 (2.8)	11 (2.5)	4 (1.5)	2 (1.0)	6 (3.1)	1 (0.5)
Abdominal pain							
All grades	2 (0.5)	2 (0.9)	8 (1.8)	4 (1.5)	4 (2.1)	2 (1.0)	1 (0.5)
Grades 3/4	1 (0.2)	2 (0.9)	6 (1.4)	3 (1.1)	3 (1.6)	2 (1.0)	1 (0.5)
General physical health deterioration							
All grades	16 (3.7)	2 (0.9)	8 (1.8)	4 (1.5)	3 (1.6)	2 (1.0)	6 (3.2)
Grades 3/4	15 (3.5)	2 (0.9)	7 (1.6)	3 (1.1)	2 (1.0)	2 (1.0)	6 (3.2)
Pain							
All grades	0	4 (1.8)	2 (0.5)	2 (0.7)	1 (0.5)	4 (2.1)	0
Grades 3/4	0	4 (1.8)	2 (0.5)	2 (0.7)	1 (0.5)	4 (2.1)	0
Back pain							
All grades	1 (0.2)	4 (1.8)	0	0	0	4 (2.1)	2 (1.1)
Grades 3/4	1 (0.2)	3 (1.4)	0	0	0	3 (1.6)	2 (1.1)

Source: ISS Table 2.3.2

Categories are not mutually exclusive. Patients with events in more than 1 category are counted once in each of those categories.
Preferred terms are sorted in descending frequency in the 'Combo 450mg QD-melanoma' column.
MedDRA Version 19.0 has been used for the reporting of adverse events.

Comparison of the Safety Profile of Combo 300 and Combo 450

The safety profile comparison is based on the 192 patients randomised to the Combo 450 arm as of the 19 May 2016 cut-off date (Part 1) and the 258 patients randomised to the Combo 300 arm (one of whom was not treated) as of the 09 November 2016 cut-off date (Part 2).

The median durations of potential follow-up for PFS of 16.7 months for Combo 450 part 1 and 13.9 months for Combo 300 part 2 were broadly comparable. The median duration of exposure in the Combo 450 arm and Combo 300 arms were similar with 52.6% and 54.9% of patients having received ≥ 48 weeks of study treatment, respectively.

In the Combo300, the median relative dose intensity (RDI) of encorafenib and binimetinib was 100% and 99.76% respectively, similar to the median RDI of encorafenib and binimetinib in the Combo450.

The overall safety profiles for the Combo 450 and Combo 300 arms are similar in terms of incidence (difference <5%) of deaths, AEs, treatment discontinuation due to AEs and AEs leading to dose modifications/ interruptions or additional therapy. The overall incidence of Grade 3-4 AEs, as well as the overall incidences of SAEs, was lower in the Combo 300 as compared to Combo 450.

Table 76: Overall Safety summary [Restricted Safety Set]

Category		Study - CMEK162B2301	
		Combo 450mg QD Cutoff Date 19MAY2016 N=192 n (%)	Combo 300mg QD Cutoff Date 09NOV2016 N=257 n (%)
Median duration of exposure:		**51.21 weeks**	**52.14 weeks**
	Grade		
On-treatment deaths [a]	All Grades	17 (8.9)	25 (9.7)
	Grade 3/4	--	--
AEs	All Grades	189 (98.4)	252 (98.1)
	Grade 3/4	111 (57.8)	120 (46.7)
Serious AEs	All Grades	66 (34.4)	75 (29.2)
	Grade 3/4	57 (29.7)	65 (25.3)
AEs leading to discontinuation	All Grades	24 (12.5)	32 (12.5)
	Grade 3/4	22 (11.5)	23 (8.9)
AEs requiring dose interruption and/or adjustment	All Grades	92 (47.9)	115 (44.7)
	Grade 3/4	63 (32.8)	59 (23.0)
AEs requiring additional therapy [b]	All Grades	165 (85.9)	211 (82.1)
	Grade 3/4	67 (34.9)	77 (30.0)

Melanoma: Naive to BRAF inhibitors and MEK inhibitors. Combo = Binimetinib + Encorafenib (doses 300 mg QD or 450 mg QD).
Combo 450 mg under Melanoma column = Restricted safety pool. All Binimetinib doses were 45 mg BID.
Abbreviations: AE=adverse event; EOT=end of treatment; PT=preferred term.
Categories are not mutually exclusive. Patients with multiple events in the same category were counted only once in that category.
Patients with events in more than 1 category were counted once in each of those categories.
[a] Deaths occurring >30 days after EOT were not included.
[b] Additional therapy includes all non-drug therapy and concomitant medications.
[*] A patient may have had both a dose interruption and a dose adjustment for a single AE PT.
[#] A patient with only a dose adjustment with no dose interruption for a single AE PT.
MedDRA Version 19.0 has been used for the reporting of adverse events.

AEs more frequent in the Combo 450 arm are shown in Table A and those more frequent in the Combo 300 arm are shown in Table B. The EAIR values were consistent with the imbalances in AE incidences between the Combo 450 vs the Combo 300 arm.

Table 77: Overall incidence of AEs (increased by ≥5%) or grade 3-4 (increased by ≥2%) in the Combo 450 arm as compared to Combo 300 arm [Restricted Safety Set]

	Combo 450mg QD Cutoff Date 19MAY2016 N=192 N% (grade 3-4%)	EAIR*	Combo 300mg QD Cutoff Date 09NOV2016 N=257 N% (grade 3-4%)	EAIR*
Any preferred term AE	**98.4(57.8)**		**98.1 (46.7)**	
Nausea	41.1(1.6)	5.03	27.2(1.6)	3.12
Diarrhoea	36.5(2.6)	4.43	28.4 (1.6)	3.43
Vomiting	29.7 (1.6)	3.05	15.2(0.4)	1.55
Fatigue	28.6 (2.1)	3.02	22.2 (0.8)	2.47
Constipation	21.9 (-)	3.05	16.7 (-)	1.75
Headache	21.9 (1.6)	2.04	11.7 (0.4)	1.15
Pyrexia	18.2(3.6)	1.69	16.7(0)	1.69

Abdominal pain	16.7(2.6)	1.57	10.5(1.2)	1.03
Vision blurred	15.6(0)	1.50	10.1(0.4)	1.02
Anaemia	15.1(4.2)	1.5	9.3 (2.7)	0.89
GGT increased	15.1 (9.4)	1.35	14 (4.7)	1.4
Dry skin	14.1 (-)	1.29	8.2 (-)	0.8
Rash	14.1 (1.0)	1.19	7.0 (0.8)	0.68
Hypertension	10.9 (5.7)	0.96	8.2 (3.5)	0.79

* EAIR (Exposure adjusted incidence rate per 100 patient-months) = (n*100)/ (total exposure time (in months) of Broad Safety Set).

Table 78: Overall incidence of AEs (increased≥5%) or grade 3-4 (increased ≥2%) increased in the Combo 300 arm as compared to Combo 450 arm [Restricted Safety Set]

	Combo 450mg QD N=192 50.64 weeks % (% grade 3-4)	**EAIR***	**Combo 300mg QD N=257 52.14 weeks % (%grade 3-4)**	**EAIR***
Back pain	9.4 (0.5)	0.8	14 (0.8)	1.39
AST increased	8.3 (2.1)	0.71	8.2 (4.3)	0.78

* EAIR (Exposure adjusted incidence rate per 100 patient-months) = (n*100)/(total exposure time (in months) of Broad Safety Set).

The increase in GI events in the Combo 450 arm did not have a big impact on the renal function; PTs of renal failure, blood creatinine increased and clinically notable shifts from baseline of creatinine lab parameter were similar in both arms. Worsening creatinine from baseline by at least 2 grades or to ≥ Grade 3 occurred for 17.7 % of patients in the Combo 300 vs 17.1% in the Combo 450. Worst post-baseline Grade 3 increased creatinine values occurred in 1.6% in the Combo 300 arm vs 3.6% in the Combo 450.

The overall incidence of SAEs was lower (difference <5%) in the Combo 300 arm as compared to Combo 450 arm (29.7% vs 34.4%). The most frequently reported SAEs that were ≥ 2.0% of patients in either treatment group occurred under the SOCs of gastrointestinal disorders (3.1% Combo 300 arm, 9.4% Combo 450), infections and infestations (6.2% Combo 300 arm, 8.9% Combo 450), general disorders and administration site conditions (3.5% Combo 300 arm, 8.3% Combo 450) and nervous system disorders (Combo 450 arm 8.2% Combo 300 arm, 7.3%).

The incidence of on-treatment deaths was similar between the treatment groups (9.7% Combo 300 arm, 9.9% Combo 450). Most on-treatment deaths were considered due to disease progression. In the Combo 300 arm and the Combo 450 group, 3 (1.2%) and 2 (1.0%) on-treatment deaths, respectively, were considered due to AEs other than disease progression (malignant melanoma/metastases).

The percentage of patients with AESIs (any grade) considered common to both drugs was higher in the Combo 450 arm compared with the Combo 300 arm (66.1% vs 51.4%). The mitigating effect of adding binimetinib to encorafenib remined evident for PTs of retinal or pigment epithelium detachment,

RVO, myopathy, muscle enzyme elevations, rash, nail disorders, and facial paresis. However, retinopathy (excluding retinal vein occlusion), rash, LFT abnormalities, haemorrhage and hypertension were more common for Combo 450 vs Combo 300.

Table 79: AESIs, Regardless of Relationship to Study Drug, by Grouping and Contribution of Each Component of the Combination– Overall, Maximum Grades 3 and 4 [Restricted Safety Set]

	Combo 450 arm QD N=192 n (%)	**Combo 300mg** QD N=257 n (%)
AESIs common to both drugs		
Any AESI N% (%Grade3-4)	**66.1 (22.9)**	**51.4 (14.8)**
Serious AESI N% (%Grade3-4)	10.4 (8.3)	6.2(4.7)
AESI leading to discontinuation N% (%Grade3-4)	5.2(3.6)	4.3(3.1)
AESI requiring dose interruption and/or change N% (%Grade3-4)	15.6(10.9)	12.5(7.8)
AESI requiring additional therapy N% (%Grade3-4)	33.3(8.3)	27.6(6.6)
Liver function test abnormalities	**48 (25.0)**	**51 (19.8)**
Grade 3/4	**28 (14.6)**	**24(9.3)**
EAIR	2.1	2.06
Rash	**50(26.0)**	**44 (17.1)**
Grade 3/4	2(1.0)	7 (2.7)
EAIR	**2.61**	0.68
Myopathy	**32(16.7)**	39 (15.2)
Grade 3/4	0	2 (0.8)
Haemorrhage	**32(16.7)**	**18 (7.0)**
Grade 3/4	0	3 (1.2)
EAIR	**1.61**	0.67
Skin infections	22(11.5)	30 (11.7)
Grade 3/4	4(2.1)	7 (2.7)
EAIR	0.88	1.15
Photosensitivity	9(4.7)	6 (2.3)
Grade 3/4	1(0.5)	0
EAIR	0.39	0.22
Acute renal failure	7 (3.6)	6 (2.3)
Grade 3/4	5(2.6)	1 (0.4)
Tachycardia	**3 (1.6)**	8 (3.1)
Grade 3/4	1(0.5)	1 (0.4)
Severe cutaneous adverse reactions	**1 (0.5)**	2 (0.8)
Grade 3/4	0	0
Nail disorders	**3 (1.6)**	4 (1.6)
Grade 3/4	0	0
Hepatic failure	**1(0.5)**	**0**
Grade 3/4	1(0.5)	0
	Combo 450 arm QD N=192 n (%)	**Combo 300mg** QD N=257 n (%)
AESIs Specific to Binimetinib		
Any AESI N% (%Grade3-4)	**69.3(18.2)**	**56.8(12.8)**
Serious AESI N% (%Grade3-4)	4.7(2.6)	2.7 (1.6)
AESI leading to discontinuation N% (%Grade3-4)	1.0(0.5)	2.3 (0.8)
AESI requiring dose interruption or change N% (%Grade3-4)	19.8(8.3)	16.7(5.1)
AESI requiring additional therapy N% (%Grade3-4)	19.3(8.3)	12.8(3.5)
Retinopathy excluding RVO	**93 (48.4)**	**79 (30.7)**
Grade 3/4	5(2.6)	4 (1.6)
EAIR	7.06	
Muscle enzyme/protein changes	**44 (22.9)**	51 (19.8)
Grade ¾	13 (6.8)	14 (5.4)

EAIR	2.20	2.13
Peripheral oedema	24(12.5)	30 (11.7)
Grade ¾	2(1.0)	9 (3.5)
EAIR	1.01	1.13
Hypertension	22(11.5)	23 (8.9)
Grade 3/4	11(5.7)	9(3.5)
EAIR	0.89	0.87
Left ventricular dysfunction	15(7.8)	15 (5.8)
Grade 3/4	3(1.6)	3 (1.2)
Venous thromboembolism	10(5.2)	5 (1.9)
Grade 3/4	2(1.0)	3 (1.2)
EAIR	0.42	0.18
Bradycardia	2(1.0)	2(0.8)
Grade 3/4	0	0
EAIR	0.08	
Pneumonitis	1(0.5)	1(0.4)
Grade 3/4	0	0
EAIR	0.04	0.04
Rhabdomyolysis	1(0.5)	0
Grade ¾	1(0.5)	0
Retinal vein occlusion	**0**	**1 (0.4)**
Grade 3/4	0	0
AESIs Specific to Encorafenib		
Any AESI N% (%Grade3-4)	14.6 (1.0)	14.4(3.1)
Serious AESI N% (%Grade3-4)	0	1.6 (1.2)
AESI leading to discontinuation N% (%Grade3-4)	0	1.6(1.2)
AESI requiring dose interruption or change N% (%Grade3-4)	4.2(1.0)	3.9(1.2)
AESI requiring additional therapy N% (%Grade3-4)	9.4(1.0)	8.9(1.9)
PPE syndrome	**13 (6.8)**	**10 (3.9)**
Grade 3/4	0	4 (1.6)
EAIR	0.57	0.36
Uveitis	7(3.6)	10 (3.9)
Grade 3/4	1(0.5)	
Cutaneous squamous cell carcinoma	5(2.6)	8 (3.1)
Grade 3/4	0	0
EAIR	0.23	0.31
Cutaneous non-squamous cell carcinoma	4 (2.1)	8 (3.1)
Grade 3/4	0	2 (0.8)
Melanomas	2 (1.0)	3 (1.2)
Grade 3/4	-	1 (0.4)
Facial paresis	**2(1.0)**	1 (0.4)
Grade 3/4	1(0.5)	0
EAIR	0.08	0.04

* EAIR (Exposure adjusted incidence rate per 100 patient-months) = (n*100)/(total exposure time (in months) of Broad Safety Set).
Source Safety appendix Table Q96E_T_6_1

Laboratory findings

Haematology

In both the Bini P and Combo 450 RP populations, decreased haemoglobin was the most common new or worsened haematology abnormality and decreases were mostly Grade 1, with no Grade 4 decreases reported (Grade 1: 47.1% vs 32.1% of patients, respectively; Grade 2: 14.2% vs 10.5%; Grade 3: 2.9% vs 4.5%). In both populations, decreases in leukocyte count and lymphocyte count were also reported in ≥10% of patients (for any CTCAE grade) but were mostly Grade 1/2. All other abnormal decreases or increases in the Combo 450 RP populations were reported in <10% of patients for any CTCAE grade, whilst decreases in neutrophil and platelet counts and increases in activated partial thromboplastin time (mostly Grade 1) were also reported in ≥10% of patients in the Bini P population.

No new or worsened haematology abnormality was reported at a higher incidence in the Combo 450 RP than in the Bini P population whilst, additionally to Grade 1 decreased haemoglobin (see above), Grade 1 activated partial thromboplastin time was reported at a higher incidence in the Bini P population than in the Combo 450 RP population.

Similarly, in both Combo 450 and vemurafenib arms of Study CMEK162B2301, decreased haemoglobin was the most common new or worsened haematology abnormality and decreases were mostly Grade 1, with no Grade 4 reported (Grade 1: 30.7% vs 36.2% of patients, respectively; Grade 2: 10.9% vs 7.3%; Grade 3: 3.7% vs 2.2%). Grade 1-3 decreased lymphocyte count was reported at a lower incidence in the Combo 450 arm than in the vemurafenib arm.

Grade 1 decreased platelet count was the only haematology abnormality reported at a higher incidence in the Combo 450 arm than in the vemurafenib arm (8.6% vs 2.8%).

Biochemistry

In both the Bini P and Combo 450 RP populations, increased creatinine was the most common new or worsened biochemistry abnormality and increases were mostly Grade 1 (Grade 1: 79.5% vs 79.2% of patients, respectively; Grade 2: 5.3% vs 15.2%; Grade 3: 0.5% vs 3%; Grade 4: 0.7% vs none).

Grade 2 increased creatinine was the only biochemistry abnormality reported at a higher incidence in the Combo 450 RP population than in the Bini P population.

Grade 1 increased ALT and AST were reported at a higher incidence in the Bini P population than in the Combo 450 RP population (40.8% vs 23.6% and 69.4% vs 25.1%) as well as Grade 3 and 4 increased CK (14.5% vs 3.4% and 8.7% vs 0.8%, respectively).

Safety in special populations

Age, gender and race

Overall, there were no clinically important effects of age on the safety of binimetinib, or on the safety of binimetinib in combination with encorafenib. Subgroups defined for the reporting of AEs were age (<65 vs ≥65 years, <75 vs >75 years), gender and race (Caucasian vs Asian vs Other) and baseline brain metastases. No clinically relevant differences were observed. No safety trends or differences were observed in this subgroup as compared to the overall patient population in Study CMEK162B2301.

Table 80: Overview of Safety according to age in Combo 450 RP

		<65 years N=194 N (%)	65-74 years N=65 N (%)	75-84 years N=14 N (%)	≥85 years N=1 N (%)
At least one TEAEs	All grades	192 (99.0)	64 (98.5)	14 (100.0)	1 (100.0)
	Grade 3-4	116 (59.8)	41 (63.1)	10 (71.4)	1 (100.0)
At least one SAEs	All grades	76 (39.2)	27 (41.5)	7 (50.0)	0 (0.0)
	Grade 3-4	64 (33.0)	23 (35.4)	7 (50.0)	0 (0.0)
Fatal	All grades	13(6.7)	2(3.1)	2(14.3)	0 (0.0)
Hospitalization/prolong existing hospitalization	All grades	58(29.9)	24(36.9)	7(50.0)	0 (0.0)
Life-threatening	All grades	4(2.1)	2(3.1)	2(14.3)	0 (0.0)
Disability/incapacity	All grades	1(0.5)	0 (0.0)	0 (0.0)	0 (0.0)

Other (medically significant)	All grades	5(2.6)	2(3.1)	0 (0.0)	0 (0.0)
AEs leading to discontinuation	All grades	20 (10.3)	6 (9.2)	5 (35.7)	1 (100.0)
	Grade 3-4	16 (8.2)	4 (6.2)	5 (35.7)	1 (100.0)
SOC Psychiatric disorders	All grades	39 (20.1)	14 (21.5)	3 (21.4)	0 (0.0)
	Grade 3-4	2 (1.0)	2 (3.1)	1 (7.1)	0 (0.0)
SOC Nervous system	All grades	92 (47.4)	33 (50.8)	9 (64.3)	1 (100.0)
	Grade 3-4	22 (11.3)	7 (10.8)	2 (14.3)	0 (0.0)
Accidents and injuries SMQ	All grades	48 (24.7)	19 (29.2)	2 (14.3)	0 (0.0)
	Grade 3-4	0 (0.0)	3 (4.6)	0 (0.0)	0 (0.0)
SOC Cardiac disorders	All grades	27 (13.9)	12 (18.5)	3 (21.4)	0 (0.0)
	Grade 3-4	1 (0.5)	1 (1.5)	2 (14.3)	0 (0.0)
SOC Vascular disorders	All grades	38 (19.6)	13 (20.0)	1 (7.1)	1 (100.0)
	Grade 3-4	10 (5.2)	6 (9.2)	0 (0.0)	0 (0.0)
SMQ Cerebrovascular disorders[a]	All grades	13 (6.7)	3 (4.6)	2 (14.3)	0 (0.0)
	Grade 3-4	8 (4.1)	2 (3.1)	1 (7.1)	0 (0.0)
SOC Infections and infestations	All grades	97 (50.0)	36 (55.4)	9 (64.3)	0 (0.0)
	Grade 3-4	18 (9.3)	8 (12.3)	0 (0.0)	0 (0.0)
Sum of following PT	All grades	32 (16.5)	15 (23.1)	4 (28.6)	0 (0.0)
	Grade 3-4	3 (1.5)	6 (9.2)	1 (7.1)	0 (0.0)
Postural Hypotensionb	All grades	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Fall	All grades	4 (2.1)	5 (7.7)	2 (14.3)	0 (0.0)
Loss of consciousness	All grades	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	All grades	1 (0.5)	1 (1.5)	0 (0.0)	0 (0.0)
Dizziness	All grades	23 (11.9)	8 (12.3)	3 (21.4)	0 (0.0)
Ataxia	All grades	1 (0.5)	1 (1.5)	0 (0.0)	0 (0.0)
Fracturec	All grades	5 (2.6)	4 (6.2)	0 (0.0)	0 (0.0)
PT Anticholinergic syndrome	All grades	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3-4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PT Quality of life decreased	All grades	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3-4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other AEs appearing more frequently in older patients[d]					
Blood alkaline phosphatase increased	All grades	8 (4.1)	8 (12.3)	3 (21.4)	1 (100.0)
	Grade 3-4	1 (0.5)	1 (1.5)	0 (0.0)	0 (0.0)
Diarrhoea	All grades	66 (34.0)	28 (43.1)	9 (64.3)	1 (100.0)
	Grade 3-4	5 (2.6)	2 (3.1)	2 (14.3)	0 (0.0)
Gamma-glutamyltransferase increased	All grades	22 (11.3)	13 (20.0)	4 (28.6)	1 (100.0)
	Grade 3-4	11 (5.7)	8 (12.3)	3 (21.4)	1 (100.0)
Pruritus	All grades	12 (6.2)	13 (20.0)	1 (7.1)	1 (100.0)
	Grade 3-4	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

Hepatic impairment

Study CMEK162A2104 was a dedicated study investigating the PK of binimetinib in hepatic impairment subjects, as defined by the NCI Organ Dysfunction Working Group, versus healthy subjects. Results indicate that, compared to healthy subjects, the exposure of binimetinib is not significantly altered in subjects with mild hepatic impairment but is increased 2-fold in subjects with moderate and severe hepatic impairment. Due to the increase in exposure observed in the moderate impairment cohort, the dose was reduced to 15 mg in the severe impairment cohort. All AEs reported in Study CMEK162A2104 were mild or moderate, except for 1 Grade 3 AE of motor vehicle accident deemed not related, and were generally consistent with previous AEs observed following binimetinib administration (headache, constipation, abdominal pain, vision blurred). Based on the results of the clinical study, the dose in moderate and severe hepatic impairment is proposed to be 30 mg BID. This dose results in a dose corresponding to 60mg BID in normal patients. The 60mg BID dose, however, was not developed further during the clinical programme as AEs were observed. No significant differences have been noted between healthy subjects and those with mild hepatic impairment, therefore, no dose adjustment is required. A hepatic impairment study has been performed. Based on these study results, popPK modelling was performed to simulate different dosing regimens for patients with moderate and severe HI. Considering total binimetinib, as 15mg TID dosing could be appropriate. However, considering the unbound drug concentrations which were impaired to a higher degree with increasing hepatic impairment, then a dose adjustment to 15mg BID was more reasonable, and it therefore proposed. Recommendations are required for dose reductions in case of adverse reactions in patients with HI.

In the Combo 450 RP population, there was no increase in notable hepatic laboratory values in the patients with liver metastases as compared with patients without liver metastases.

Renal impairment

The effect of renal impairment on binimetinib exposure was assessed in a dedicated clinical study with an abbreviated design (Study ARRAY-162-106). Results from the severe impairment cohort (eGFR ≤29 mL/min/1.73 m2), indicate an approximate 29% increase in exposure (AUCinf) and 21% increase in Cmax compared to matching healthy subjects. Based on the results in the severely-impaired cohort compared to matching healthy subjects in Study ARRAY-162-106, no dose adjustment is required in subjects with renal impairment.

The following subgroup analyses were also performed:

• Hepatic lab test abnormalities– in the Combo 450 RP population there was no increase in notable hepatic laboratory values in the patients with liver metastases as compared with patients without liver metastasis. In the Bini P population, more patients with liver metastases had notable hepatic laboratory values (ALT, AST, ALP) as compared with the overall population and patients with no liver metastases; however, there were still limited numbers of patients overall with notable hepatic laboratory values.

• LVEF – in the Combo 450 RP population, there was no difference in the incidence of “worst change from baseline” in LVEF between those with or without baseline risk factors (cardiac risk, hypertension, LVD risk) and a small difference in the incidence of “shift” in LVEF, with more Combo 450-treated patients without baseline risk factors having Grade 2/3 shifts than patients with baseline risk factors.

• Cardiac enzymes – more Combo 450-treated patients who did not receive concomitant statin treatment had a 2-Grade worst shift in CK than patients who did receive concomitant statin treatment.

Safety related to drug-drug interactions and other interactions

The applicant did not submit data on the safety related to drug-drug interaction (see clinical safety discussion).

See section on Pharmacokinetic interaction studies and Pharmacokinetic using biomaterials.

Discontinuation due to adverse events

AEs leading to study drug discontinuation

Adverse Events Leading to Study Drug Discontinuation in the Broad Safety Set

Table 81 presents a summary of AEs leading to study drug discontinuation, regardless of relationship to study drug, that were reported for ≥1% of patients in any population by PT (overall and maximum Grade 3/4) for the Broad Safety Set.

Table 81: Adverse Events Leading to Study Drug Discontinuation, Regardless of Study Drug Relationship, by Preferred Term and Treatment – Overall and Maximum Grade 3 or 4 (any grade and Grade 3/4 AE ≥1% in any population) (Broad Safety Set)

	Melanoma				Study CMEK162B2301		
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 (%)
All grades	103 (24.1)	38 (17.5)	45 (10.4)	28 (10.2)	24 (12.5)	27 (14.1)	31 (16.7)
Grades 3/4	70 (16.4)	29 (13.4)	33 (7.6)	24 (8.8)	22 (11.5)	21 (10.9)	18 (9.7)
ALT increased	4 (0.9)	0	8 (1.8)	5 (1.8)	5 (2.6)	0	2 (1.1)
Grades 3/4	3 (0.7)	0	5 (1.2)	4 (1.5)	4 (2.1)	0	2 (1.1)
AST increased	4 (0.9)	0	8 (1.8)	5 (1.8)	5 (2.6)	0	2 (1.1)
Grades 3/4	4 (0.9)	0	3 (0.7)	2 (0.7)	2 (1.0)	0	2 (1.1)
Blood creatinine increased	0	0	5 (1.2)	3 (1.1)	2 (1.0)	0	0
GGT increased	0	1 (0.5)	2 (0.5)	2 (0.7)	2 (1.0)	1 (0.5)	3 (1.6)
Grades 3/4	0	1 (0.5)	1 (0.2)	1 (0.4)	1 (0.5)	1 (0.5)	3 (1.6)
Headache	0	2 (0.9)	2 (0.5)	2 (0.7)	2 (1.0)	2 (1.0)	1 (0.5)
Grades 3/4	0	2 (0.9)	1 (0.2)	1 (0.4)	1 (0.5)	2 (1.0)	0
Blood CK increased	8 (1.9)	0	2 (0.5)	1 (0.4)	1 (0.5)	0	0
Grades 3/4	8 (1.9)	0	0	0	0	0	0
Diarrhoea	2 (0.5)	2 (0.9)	2 (0.5)	1 (0.4)	1 (0.5)	2 (1.0)	0
Grades 3/4	1 (0.2)	2 (0.9)	2 (0.5)	1 (0.4)	1 (0.5)	2 (1.0)	0
Metastases to CNS	0	2 (0.9)	1 (0.2)	1 (0.4)	1 (0.5)	2 (1.0)	0
Rash	4 (0.9)	1 (0.5)	1 (0.2)	1 (0.4)	1 (0.5)	1 (0.5)	2 (1.1)
Arthralgia	0	1 (0.5)	0	0	0	1 (0.5)	3 (1.6)
Dermatitis acneiform	5 (1.2)	0	0	0	0	0	0
Ejection fraction decreased	16 (3.7)	2 (0.9)	1 (0.2)	0	0	2 (1.0)	0
Grades 3/4	8 (1.9)	2 (0.9)	0	0	0	2 (1.0)	0
Facial paralysis	0	2 (0.9)	0	0	0	2 (1.0)	0
General physical health deterioration	5 (1.2)	0	1 (0.2)	0	0	0	1 (0.5)
Grades 3/4	5 (1.2)	0	1 (0.2)	0	0	0	1 (0.5)
Hepatotoxicity	0	0	0	0	0	0	2 (1.1)
Grades 3/4	0	0	0	0	0	0	2 (1.1)
Hypersensitivity	0	2 (0.9)	0	0	0	2 (1.0)	1 (0.5)
Nausea	2 (0.5)	0	0	0	0	0	2 (1.1)
Oedema peripheral	5 (1.2)	0	0	0	0	0	0
PPE syndrome	1 (0.2)	8 (3.7)	0	0	0	5 (2.6)	0
Grades 3/4	0	4 (1.8)	0	0	0	3 (1.6)	0
Photosensitivity reaction	0	0	0	0	0	0	3 (1.6)
Retinal vein occlusion	7 (1.6)	0	0	0	0	0	0
Grades 3/4	5 (1.2)	0	0	0	0	0	0
Vomiting	2 (0.5)	3 (1.4)	2 (0.5)	0	0	3 (1.6)	1 (0.5)
Grades 3/4	1 (0.2)	2 (0.9)	2 (0.5)	0	0	2 (1.0)	0

Source: ISS Table 2.4.2
Categories are not mutually exclusive. Patients with events in more than 1 category are counted once in each of those categories.
Preferred terms are sorted in descending frequency in the 'Combo 450mg QD-melanoma' column.
AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma glutamyl transferase, CK: creatine kinase, CNS: central nervous system

Bini P vs Combo 450 RP (pooled sets)

The incidences of overall and Grade 3/4 AEs leading to study drug discontinuation were lower in the Combo 450 RP population compared to the Bini P population (AEs: 10.2% vs 24.1%; Grade 3/4 AEs: 8.8% vs 16.4%).

There were no AEs leading to study drug discontinuation reported in ≥2% of patients in the Combo 450 RP population and the only Grade 3/4 AE leading to study drug discontinuation reported in ≥1% of patients was ALT increased (1.5%).

Adverse Events Leading to Dose Interruption or Adjustment

Table 82 presents a summary of AEs requiring dose adjustment or study-drug interruption, regardless of relationship to study drug, that were reported in ≥5% of patients for AEs of any grade and in ≥2% of patients for AEs of Grade 3/4 in any population by PT for the Broad Safety Set.

Table 82: Adverse Events Requiring Dose Adjustment or Study-drug Interruption, Regardless of Study Drug Relationship, by Preferred Term and Treatment - Overall and Maximum Grade 3 or 4 (any grade ≥5% or Grade 3/4 AE≥2% in any population) (Broad Safety Set)

	Melanoma				Study CMEK162B2301		
Preferred Term Grades	Bini 45mg BID N=427 n (%)	Enco 300mg QD N=217 n (%)	Combo pooled doses N=433 n (%)	Combo 450mg QD N=274 n (%)	Combo 450mg QD N=192 n (%)	Enco 300mg QD N=192 n (%)	Vemurafenib N=186 n (%)
Any preferred term							
All grades	285 (66.7)	152 (70.0)	212 (49.0)	130 (47.4)	92 (47.9)	135 (70.3)	114 (61.3)
Grades 3/4	176 (41.2)	93 (42.9)	142 (32.8)	88 (32.1)	63 (32.8)	85 (44.3)	71 (38.2)
Nausea							
All grades	18 (4.2)	17 (7.8)	26 (6.0)	18 (6.6)	16 (8.3)	17 (8.9)	14 (7.5)
Grades 3/4	3 (0.7)	5 (2.3)	6 (1.4)	4 (1.5)	3 (1.6)	5 (2.6)	2 (1.1)
Vomiting							
All grades	19 (4.4)	10 (4.6)	23 (5.3)	16 (5.8)	13 (6.8)	10 (5.2)	4 (2.2)
Grades 3/4	5 (1.2)	4 (1.8)	3 (0.7)	2 (0.7)	1 (0.5)	4 (2.1)	1 (0.5)
Ejection fraction decreased							
All grades	26 (6.1)	0	18 (4.2)	14 (5.1)	10 (5.2)	0	0
Grades 3/4	5 (1.2)	0	3 (0.7)	2 (0.7)	2 (1.0)	0	0
GGT increased							
All grades	1 (0.2)	5 (2.3)	11 (2.5)	10 (3.6)	9 (4.7)	4 (2.1)	2 (1.1)
Grades 3/4	1 (0.2)	3 (1.4)	10 (2.3)	9 (3.3)	9 (4.7)	3 (1.6)	0
Pyrexia							
All grades	10 (2.3)	5 (2.3)	19 (4.4)	10 (3.6)	8 (4.2)	5 (2.6)	14 (7.5)
Grades 3/4	0	2 (0.9)	5 (1.2)	4 (1.5)	4 (2.1)	2 (1.0)	0
ALT increased							
All grades	7 (1.6)	4 (1.8)	30 (6.9)	15 (5.5)	7 (3.6)	4 (2.1)	4 (2.2)
Grades 3/4	4 (0.9)	2 (0.9)	17 (3.9)	8 (2.9)	6 (3.1)	2 (1.0)	1 (0.5)
AST increased							
All grades	10 (2.3)	2 (0.9)	24 (5.5)	10 (3.6)	6 (3.1)	2 (1.0)	3 (1.6)
Grades 3/4	2 (0.5)	0	9 (2.1)	2 (0.7)	1 (0.5)	0	1 (0.5)
Blood CK increased							
All grades	80 (18.7)	0	11 (2.5)	8 (2.9)	6 (3.1)	0	1 (0.5)
Grades 3/4	65 (15.2)	0	6 (1.4)	4 (1.5)	3 (1.6)	0	0
Diarrhoea							
All grades	24 (5.6)	4 (1.8)	18 (4.2)	11 (4.0)	7 (3.6)	4 (2.1)	9 (4.8)
Grades 3/4	4 (0.9)	0	5 (1.2)	3 (1.1)	1 (0.5)	0	3 (1.6)
Abdominal pain							
All grades	3 (0.7)	3 (1.4)	10 (2.3)	7 (2.6)	5 (2.6)	3 (1.6)	2 (1.1)
Grades 3/4	0	1 (0.5)	4 (0.9)	3 (1.1)	3 (1.6)	1 (0.5)	0
Anaemia							
All grades	2 (0.5)	2 (0.9)	8 (1.8)	4 (1.5)	4 (2.1)	2 (1.0)	2 (1.1)
Grades 3/4	2 (0.5)	2 (0.9)	5 (1.2)	2 (0.7)	2 (1.0)	2 (1.0)	1 (0.5)
Blood alkaline phosphatase increased							
All grades	1 (0.2)	1 (0.5)	8 (1.8)	7 (2.6)	4 (2.1)	1 (0.5)	1 (0.5)
Grades 3/4	0	0	3 (0.7)	2 (0.7)	1 (0.5)	0	0
Blood creatinine increased							
All grades	0	0	11 (2.5)	6 (2.2)	4 (2.1)	0	4 (2.2)
Grades 3/4	0	0	0	0	0	0	1 (0.5)
Hyperkeratosis							

Preferred Term Grades	Melanoma Bini 45mg BID N=427 n (%)	Melanoma Enco 300mg QD N=217 n (%)	Melanoma Combo pooled doses N=433 n (%)	Melanoma Combo 450mg QD N=274 n (%)	Study CMEK162B2301 Combo 450mg QD N=192 n (%)	Study CMEK162B2301 Enco 300mg QD N=192 n (%)	Study CMEK162B2301 Vemurafenib N=186 n (%)
All grades	0	16 (7.4)	4 (0.9)	4 (1.5)	4 (2.1)	10 (5.2)	2 (1.1)
Grades 3/4	0	9 (4.1)	1 (0.2)	1 (0.4)	1 (0.5)	6 (3.1)	0
Arthralgia							
All grades	1 (0.2)	26 (12.0)	10 (2.3)	6 (2.2)	4 (2.1)	24 (12.5)	16 (8.6)
Grades 3/4	1 (0.2)	16 (7.4)	4 (0.9)	1 (0.4)	0	14 (7.3)	8 (4.3)
Fatigue							
All grades	10 (2.3)	6 (2.8)	12 (2.8)	6 (2.2)	4 (2.1)	4 (2.1)	7 (3.8)
Grades 3/4	7 (1.6)	2 (0.9)	4 (0.9)	4 (1.5)	2 (1.0)	1 (0.5)	2 (1.1)
Hypertension							
All grades	15 (3.5)	1 (0.5)	7 (1.6)	6 (2.2)	4 (2.1)	1 (0.5)	2 (1.1)
Grades 3/4	12 (2.8)	1 (0.5)	7 (1.6)	6 (2.2)	4 (2.1)	1 (0.5)	1 (0.5)
Lipase increased							
All grades	2 (0.5)	1 (0.5)	14 (3.2)	6 (2.2)	3 (1.6)	1 (0.5)	0
Grades 3/4	2 (0.5)	1 (0.5)	14 (3.2)	6 (2.2)	3 (1.6)	1 (0.5)	0
Retinal detachment							
All grades	18 (4.2)	1 (0.5)	6 (1.4)	5 (1.8)	4 (2.1)	1 (0.5)	1 (0.5)
Grades 3/4	0	0	2 (0.5)	1 (0.4)	1 (0.5)	0	0
Amylase increased							
All grades	2 (0.5)	0	9 (2.1)	4 (1.5)	2 (1.0)	0	0
Grades 3/4	2 (0.5)	0	5 (1.2)	3 (1.1)	2 (1.0)	0	0
Rash							
All grades	31 (7.3)	7 (3.2)	3 (0.7)	3 (1.1)	3 (1.6)	7 (3.6)	14 (7.5)
Grades 3/4	11 (2.6)	3 (1.4)	1 (0.2)	1 (0.4)	1 (0.5)	3 (1.6)	6 (3.2)
Headache							
All grades	0	12 (5.5)	3 (0.7)	3 (1.1)	2 (1.0)	12 (6.3)	2 (1.1)
Grades 3/4	0	1 (0.5)	2 (0.5)	2 (0.7)	1 (0.5)	1 (0.5)	0
Palmar-plantar erythrodysaesthesia syndrome							
All grades	1 (0.2)	49 (22.6)	4 (0.9)	3 (1.1)	1 (0.5)	48 (25.0)	3 (1.6)
Grades 3/4	1 (0.2)	22 (10.1)	0	0	0	22 (11.5)	2 (1.1)
Abdominal pain upper							
All grades	1 (0.2)	5 (2.3)	3 (0.7)	2 (0.7)	2 (1.6)	5 (2.6)	2 (1.1)
Grades 3/4	0	1 (0.5)	1 (0.4)	1 (0.4)	1 (0.5)	1 (0.5)	0
Asthenia							
All grades	12 (2.8)	9 (4.1)	2 (0.5)	2 (0.7)	2 (1.0)	7 (3.6)	7 (3.8)
Grades 3/4	2 (0.5)	4 (1.8)	0	0	0	3 (1.6)	5 (2.7)
Decreased appetite							
All grades	1 (0.2)	3 (1.4)	4 (0.9)	2 (0.7)	2 (1.0)	3 (1.6)	7 (3.8)
Grades 3/4	0	0	1 (0.2)	0	0	0	1 (0.5)
Pain in extremity							
All grades	0	7 (3.2)	2 (0.5)	2 (0.7)	1 (0.5)	7 (3.6)	4 (2.2)
Grades 3/4	0	1 (0.5)	1 (0.2)	1 (0.4)	0	1 (0.5)	0
Dermatitis acneiform							
All grades	28 (6.6)	2 (0.9)	1 (0.2)	1 (0.4)	1 (0.5)	2 (1.0)	1 (0.5)
Grades 3/4	7 (1.6)	0	0	0	0	0	0
Dyspnoea							
All grades	11 (2.6)	0	2 (0.5)	1 (0.4)	1 (0.5)	0	2 (1.1)
Grades 3/4	2 (0.5)	0	1 (0.2)	0	0	0	0
Facial paralysis							
All grades	0	5 (2.3)	1 (0.2)	1 (0.4)	1 (0.5)	4 (2.1)	0
Grades 3/4	0	1 (0.5)	1 (0.2)	1 (0.4)	1 (0.5)	1 (0.5)	0

Preferred Term Grades	Melanoma Bini 45mg BID N=427 n (%)	Melanoma Enco 300mg QD N=217 n (%)	Melanoma Combo pooled doses N=433 n (%)	Melanoma Combo 450mg QD N=274 n (%)	Study CMEK162B2301 Combo 450mg QD N=192 n (%)	Study CMEK162B2301 Enco 300mg QD N=192 n (%)	Study CMEK162B2301 Vemurafenib N=186 n (%)
General physical health deterioration							
All grades	5 (1.2)	2 (0.9)	1 (0.2)	1 (0.4)	1 (0.5)	2 (1.0)	5 (2.7)
Grades 3/4	2 (0.5)	2 (0.9)	1 (0.2)	1 (0.4)	1 (0.5)	2 (1.0)	4 (2.2)
Myalgia							
All grades	10 (2.3)	25 (11.5)	1 (0.2)	1 (0.4)	1 (0.5)	24 (12.5)	3 (1.6)
Grades 3/4	2 (0.5)	18 (8.3)	0	0	0	17 (8.9)	0
Oedema peripheral							
All grades	19 (4.4)	3 (1.4)	2 (0.5)	1 (0.4)	1 (0.5)	2 (1.0)	1 (0.5)
Grades 3/4	0	0	1 (0.2)	1 (0.4)	1 (0.5)	0	0
Rash generalised							
All grades	0	3 (1.4)	1 (0.2)	0	0	3 (1.6)	10 (5.4)
Grades 3/4	0	1 (0.5)	1 (0.2)	0	0	1 (0.5)	7 (3.8)
Rash maculo-papular							
All grades	4 (0.9)	4 (1.8)	0	0	0	4 (2.1)	10 (5.4)
Grades 3/4	3 (0.7)	1 (0.5)	0	0	0	1 (0.5)	7 (3.8)

Source: ISS Table 2.4.4

Categories are not mutually exclusive. Patients with events in more than 1 category are counted once in each of those categories.
Preferred terms are sorted in descending frequency in the 'Combo 450mg QD-melanoma' column.
MedDRA Version 19.0 has been used for the reporting of adverse events.

Post marketing experience

The applicant did not submit post-marketing data as the product has not been marketed.

2.6.1. Discussion on clinical safety

Currently, safety data for binimetinib is assessable from a total of 2555 healthy subjects and patients. They have received at least 1 dose of binimetinib including 220 healthy subjects, 164 patients with rheumatoid arthritis, 12 patients with hepatic dysfunction and 2159 patients with advanced cancer have received at least one dose.

Safety data from a total of 860 patients with unresectable or metastatic melanoma are presented. Binimetinib 45 mg BID as monotherapy was evaluated in 427 patients with metastatic melanoma with 7% of patients receiving ≥48 weeks of study treatment. The recommended combination dose of binimetinib 45mg BID and encorafenib 450 mg QD (Combo 450) was evaluated in 274 patients treated for metastatic melanoma with 44.2% of patients receiving ≥48 weeks of study treatment. The overall size of the safety data set and the extent of exposure are sufficient to characterise the safety of binimetinib at the dose of 45 mg BID as monotherapy and in combination with encorafenib 450 mg QD. Combo 450 is intended for treatment of advanced or metastatic *BRAF*-mutated melanoma, a serious and life-threatening condition.

Furthermore, a "broad combination safety pool" (Combo BP) was defined which includes pooled data from 437 patients with BRAF V600-mutant metastatic melanoma enrolled at or randomized to a dose of 45 mg BID binimetinib plus various doses of encorafenib, ranging from 400 mg QD to 600 mg QD (192 patients from Study CMEK162B2301 [Part 1], 158 patients from Study CLGX818X2109 and 87 patients from Study CMEK162X2110).

For this submission, the restricted combination safety pool (Combo 450 RP) and the binimetinib monotherapy safety pool (Bini P) provide the most clinical relevant safety data.

The median duration of exposure to study treatment was respectively 13.0 weeks in the bini P population (mostly NRAS mutant melanoma) and 41.9 weeks in the Combo 450 RP BRAF melanoma population. The median duration of exposure to study treatment was longer in the Combo 450 arm than in the encorafenib and vemurafenib arms of Study CMEK162B2301, (51.2 weeks vs 31.4 weeks vs 27.1 weeks).

Despite the higher dose intensity and more than 3 times longer duration of exposure in Combo 450 patients compared with Bini P population, a better tolerability of Combo 450 vs binimetinib alone was observed. A lower percentage of patients experienced at least one, grade3/4 AE (58.0% vs 66.7%), AE leading to treatment discontinuation (10.2% vs 24.1%), AE requiring dose interruption/change (47.4% vs 66.7%) and AE requiring additional therapy (86.1% vs 92.3%). The percentage of patients who experienced at least one SAE was similar in the two populations, (35.8% vs 33.0%), regardless of causal relationship to study drugs.

In Study CMEK162B2301, despite a 50% longer median duration of treatment in the Combo 450 arm than in the vemurafenib arm, a better tolerability of Combo 450 vs vemurafenib alone was observed. A lower percentage of patients experienced at least one, grade 3/4 AE (57.8% vs. 63.4%), AE leading to treatment discontinuation (12.5% vs 16.7%), AE requiring dose interruption/reduction (47.9% vs 61.3%) and AE requiring additional therapy (85.9% vs 91.9%). In addition, a similar percentage of patients experienced SAEs (34.4% vs 37.1%).

Similarly, in Study CMEK162B2301, despite a 60% longer median duration of treatment in the Combo 450 arm compared to the Enco 300 arm a better tolerability of Combo 450 vs Enco 300 alone was observed. A lower percentage of patients experienced at least, one grade 3/4 AE (57.8% vs 66.1%), AE leading to treatment discontinuation (12.5% vs 14.1%), AE requiring dose interruption/change (47.9% vs 70.3%) and AE requiring additional therapy (85.9% vs 94.3%). The percentage of patients who experienced at least one SAE was similar (34.4% vs 33.9%) in the two populations, regardless of causal relationship to study drugs.

There is no study with a direct comparison of Combo 450 and binimetinib 45 mg BID, however indirect comparison showed a more favourable tolerability profile for Combo 450 than that reported for binimetinib 45 mg BID monotherapy. The overall incidence of AEs and SAEs was similar between the Combo 450 RP population and Bini P population but a lower proportion of patients in the Combo 450 RP population reported Grade 3/4 AEs (58% vs 66.3%). In addition, in the Combo 450 RP population, a lower proportion of patients compared to the Bini P population reported AEs leading to treatment discontinuation, AEs requiring dose interruption or additional therapy (discontinuation: 10.2% vs 22.5%; interruption: 47.1% vs 66.3%, additional therapy 86.1%vs 92.3%). On-treatment deaths were reported in a similar proportion of patients in both arms. The median time to onset of first AEs resp. SAEs was longer in the combination population than in the binimetinib monotherapy population.

The safety and tolerability of binimetinib in combination with encorafenib appear favourable and acceptable as compared to vemurafenib regarding the observed benefit. The majority of the reported ADRs reflects the common AEs observed in the clinical programme of binimetinib 45 mg BID monotherapy and binimetinib 45 mg BID given in combination with encorafenib 450 mg QD. The addition of binimetinib 45 mg BID in the combination allows for the administration of encorafenib at the dose of 450 mg QD. The observed toxicities of the combination are generally manageable and acceptable in the population of adult patient with metastatic or unresectable melanoma harbouring a BRAF mutation, and no prior therapy.

A comparison of the safety results of Combo 450 in Study CMEK162B2301 with those of the recently approved BRAF/MEK inhibitor combinations vemurafenib/cobimetinib and dabrafenib/trametinib in pivotal Phase 3 studies is presented in the table below. The studies were broadly comparable in terms of the demographic and disease characteristics of patient populations and in terms of study design. Vemurafenib, the comparator used in Study CMEK162B2301 had a safety profile similar to that of other trials using vemurafenib as a comparator[15],[17], [23]). For the combination, similar rates of AEs overall, grade ≥3 AEs treatment-related AEs, serious AEs, and AEs leading to death, or to dose interruptions/modifications or to treatment discontinuation compared to COMBI-v and similar or higher incidences of these events in Study CMEK162B2301 compared to coBRIM.

A 4-month update of the safety profile was provided with the responses. The updated safety data provided with additional follow-up shows a similar safety profile for the Combo 450 as demonstrated in the initial submission. New ADRs of blood creatinine increased, renal failure and GGT increased for encorafenib in combination with binimetinib, and blood creatinine increased for encorafenib single agent, have been added to the proposed SmPC since the initial submission.

Combo 450 vs Combo 300

The median duration of exposure in the Combo 450 and Combo 300 arms were similar with, respectively, 52.6% and 54.9% of patients having received ⩾ 48 weeks of study treatment.

[23] Daud A, Gill J, Kamra S, Chen L, Ahuja A. Indirect treatment comparison of dabrafenib plus trametinib versus vemurafenib plus cobimetinib in previously untreated metastatic melanoma patients. J Hematol Oncol. 2017 Jan 4;10(1):3

The overall tolerability profiles of these two combinations were broadly similar (for AEs requiring discontinuation, dose modifications or additional therapy) but Combo 450 led to an increased incidence of SAEs and Grade 3-4 AEs. Combo 450 generated an increased incidence of the most common side effects compared to Combo 300, particularly nausea (41.1 vs. 27.2%), vomiting (29.7 vs. 15.2) and headache (21.9 vs. 11.7%).

The median time to onset of key tolerability parameters was longer in the Combo 300 arm compared with the Combo 450 arm for:

- First SAE (3.5 vs 4.7 months respectively)

- First AE resulting in study drug discontinuation (3.8 vs 4.7 months respectively)

The percentage of patients with one or more encorafenib AESI (any grade) was similar in the two populations (14.6% vs 14.4%). Surprisingly, the percentage of patients with one or more binimetinib specific AESIs (any grade) was higher too in the Combo 450 arm compared with the Combo 300 arm (69.3% vs 56.8% respectively). However, the incidence of binimetinib specific AESIS leading to drug discontinuation or drug modification were similar between Combo 450 and Combo 300. This may be due to a rather arbitrary allocation of AESI between encorafenib and binimetinib in the original assessment, which has since been changed/ rectified. Retinopathy (excluding retinal vein occlusion), rash, liver function tests (LFT) abnormalities, haemorrhage and hypertension were more common for Combo 450 vs Combo 300.

This is comparison of Combo 450 vs. Combo 300 is a *post-hoc* analysis and patients were recruited at different times (30 Dec 2013 to 10 Apr 2015 for Combo 450 and 19 March 2015 to 12 Nov 2015 for Combo 300). It is possible that investigators had more experience in treating/ preventing AEs by the time of recruitment to Combo 300; given that different centres participated in Part 1 and Part 2 of the study it is more likely that the difference is simply due to the encorafenib dose.

As for other MEK and BRAF inhibitors[24], several main toxicities are presumed to be class effects and are defined as AESIs for the clinical development of binimetinib and encorafenib.

The AESI groupings common to both binimetinib and encorafenib reported and analysed include the following:

Ocular AESI groupings: retinopathy (mainly due to binimetinib) excluding RVO, RVO and uveitis-type events (mainly due to encorafenib)

- Dermatologic-related AESI groupings: rash (photosensitivity, nail disorders, skin infections, severe cutaneous adverse reactions) and PPE syndrome (mainly due to encorafenib)
- Liver-related AESI groupings: liver function test abnormalities and hepatic failure
- Myopathy/rhabdomyolysis-related AESI groupings: muscle enzyme/protein changes (mainly due to binimetinib), myopathy and rhabdomyolysis (mainly due to encorafenib)

The AESI groupings relating to binimetinib alone reported and analysed in this Application include the following:

- Cardiac-related AESI groupings: (bradycardia) and left ventricular dysfunction;
- Hypertension
- Haemorrhage

[24] Daud A, Tsai K. Management of Treatment-Related Adverse Events with Agents Targeting the MAPK Pathway in Patients with Metastatic Melanoma. Oncologist. 2017 Jul;22(7):823-833

- (Peripheral oedema)
- Pneumonitis
- (Venous thromboembolism)

The AESI groupings relating to encorafenib alone reported and analysed in this Application include the following:

- (Tachycardia)
- Acute renal failure
- (Facial paresis)
- Cutaneous malignancies AESI groupings: cutaneous squamous cell carcinoma, cutaneous non-squamous cell carcinoma and melanomas

Regarding the incidences and severities of the known BRAF and MEK inhibitor AESIs, the tolerability of the MEK inhibitor binimetinib seems to be remarkably better when given in combination with the BRAF inhibitor encorafenib.

However, the incidence of retinopathies, liver function test abnormalities and haemorrhage events seems to be higher. This point should be kept in mind as these AESIs (at least retinopathies and liver function test abnormalities) resulted in the reduction of the RP2D to 45 mg BID in the binimetinib monotherapy. Preliminary data of part 2 of the pivotal study indicate a better tolerability in the Combo 300mg population regarding retinopathies, liver function test abnormalities and haemorrhage events.

Specifically, for binimetinib, the most important risks associated with binimetinib treatment defined by ADRs in the proposed patient population are described below. This includes data from monotherapy trials conducted for binimetinib. Descriptions of the events during use in combination with encorafenib are also included below.

RPED and RVO:

The ocular toxicities of binimetinib can in rare instances be sight threatening although no cases of permanent blindness have been reported. Visual impairment, including vision blurred and reduced visual acuity, occurred in 13% (56/427) of patients and was generally reversible. RPED is a characteristic adverse effect of MEK inhibition and was closely monitored in the binimetinib clinical program. While evidence of retinopathy was detected frequently, in 31.6% of patients treated at the recommended dose, i.e., all melanoma binimetinib 45 mg group, it was often asymptomatic (grade 1 in 18% of patients) or mildly symptomatic (grade 2 in 12% of patients) and could be managed without need for dose modification. RVO was seen infrequently (1.6% [9/566 patients in the all cancers (binimetinib any dose) population]), but is a potentially sight-threatening event. Patients with RVO were discontinued from treatment with binimetinib and the majority with available follow-up showed evidence of recovery. The safety of binimetinib has not been established in patients with a history of or current evidence of RVO or current risk factors for RVO including uncontrolled glaucoma, or a history of hyperviscosity or hypercoagulability syndromes. Binimetinib must be discontinued with the occurrence of RVO. Binimetinib is not recommended in patients with a history of RVO.

In comparison with Binimetinib monotherapy (Bini P) there was a higher incidence of retinal events in the combination arm (Combo 450 RP) but this tendency was reversed when considering adjustment for study drug exposure. However, regarding the PTs, retinal detachment was reported at a higher incidence for the binimetinib monotherapy (10.3% Bini vs 6.6% Combo), vision blurred for the combination therapy (15.3% Combo vs 6.6% Bini). However, in summary, an additive adverse effect

of binimetinib and encorafenib regarding Retinopathy can be suggested. In addition, in 3 patients (in the pivotal study CMEK162B2301 Part 1) events under the PT of blindness (in the grouping of retinopathy excluding RVO) were reported (2 patients in the Combo 450 arm and 1 patient in the encorafenib Part 1 arm). In the binimetinib monotherapy population no cases of blindness were reported.

In the Vemurafenib-Arm ocular events were only reported with a low incidence. However, it should be kept in mind that for the combination of vemurafenib and cobimetinib a similar incidence of ocular events was reported as for Combo 450 RP.

Vascular eye events (RVO) as potentially sight–threatening events were seen only in the Binimetinib arm. In contrast uveitis-Type AESIs were mainly reported for the combination but only in a quite low incidence and in a mild severity.

See section 4.4 for further information on special warnings and precautions of use concerning ocular toxicities.

Skin-related "rash" events

These were observed very common and reported in 81.4 % of patients treated with binimetinib monotherapy. Most cases were grade 1 or 2 severity but 68% were requiring additional therapy. Considering that these events often results in an impairment of infection protection and the binimetinib is also a TNF inhibitor, the increase rates of infections and cases of sepsis observed may be also seen as drug related complications. As the median time of onset was 0.4 month for these events, more clarification of potential dangerous consequences of these very frequent events and early occurring AE is needed.

Rash has been identified as an AESI for encorafenib and binimetinib and is a known class effect of both, BRAF and MEK inhibitors. Rash is among the most frequently observed AEs reported with these two classes of agents when used as single agents (Bini P 82.7%, Enco P 51.2%) and is reported at a lower frequency when these 2 classes of agents are combined (Combo 450 RP 23.7%). Compared to other MEK/BRAF inhibitors the incidence of rash seems to be lower for the combination therapy with binimetinib/ encorafenib. In addition, the presented data of part 2 of the pivotal study indicates a better tolerability in the Combo 300 mg population.

Palmar-plantar erythrodysaesthesia syndrome (PPES) has been identified as an AESI for both encorafenib and binimetinib as these types of dermatologic complications are known class effects reported with the use of BRAF inhibitors. In addition, these reactions have also been reported with MEK inhibitors but less frequently. The incidence of PPES was obviously lower in the combination therapy than in the encorafenib monotherapy.

Dermatologic "non-rash" events:

These occurred in 42.4% of patients with binimetinib monotherapy. The median time of onset of this toxicity was 1.4-month, additional therapy was required in 24%. In addition, approx. 25% of the patients showed - often secondary to other dermatologic events- a skin infection; 3.3% of these events were resulting in hospitalization.

New primary malignancies

New primary malignancies, cutaneous and non-cutaneous, have been observed in patients treated with BRAF inhibitors and can occur when binimetinib is administered in combination with encorafenib (see section 4.8).

Cutaneous malignancies

The combination of binimetinib to encorafenib appeared to attenuate the development of cutaneous squamous cell carcinoma (cuSCC) as compared to encorafenib treatment alone. Cutaneous non-squamous cell carcinoma (cnSCC) events were reported in a low percentage of patients overall (2.1% Combo 450 arm, 1.0% encorafenib Part 1 arm). No Melanoma events were reported in the Combo 450 populations and in the Bini P population while in the encorafenib Part 1 and vemurafenib monotherapy arms, melanoma events occurred in a similar percentage of patients (5.2% encorafenib Part 1 arm, 4.3% vemurafenib arm).

Cutaneous malignancies such as cutaneous squamous cell carcinoma (cuSCC) including kerathoacanthoma has been observed in patients treated with binimetinib when used in combination with encorafenib.

Dermatologic evaluations should be performed prior to initiation of therapy with binimetinib in combination with encorafenib, every 2 months while on therapy and for up to 6 months following discontinuation of the combination. Suspicious skin lesions should be managed with dermatological excision and dermatopathologic evaluation. Patients should be instructed to immediately inform their physicians if new skin lesions develop. Binimetinib and encorafenib should be continued without any dose modifications.

In summary, the addition of Binimetinib (MEK inhibitor) to encorafenib seems to mitigate the risks of secondary skin neoplasms, in the Combo 450 population (compared to the Combo 300 population).

Liver related events:

Liver laboratory abnormalities

Liver enzyme abnormalities are also common (ALT in 9.6%; AST in 13.6% of patients treated at the recommended dose) with binimetinib treatment. Although liver enzyme monitoring was enhanced as a result of a case of hepatic failure in a single patient treated at the 60 mg BID dose of binimetinib, the applicant states that no Hy's law cases or other clear cases of drug-induced liver injury have been observed at the recommended 45 mg BID dose. Liver laboratory abnormalities including AST and ALT elevations can occur with binimetinib (see section 4.8). Liver laboratory values should be monitored before initiation of binimetinib and encorafenib and at least monthly during the 6 first months of treatment, and then as clinically indicated. Liver laboratory abnormalities should be managed with dose interruption, reduction or treatment discontinuation (see Table 1 in section 4.2).

With respect to overall tolerability hepatotoxicity observed indicate a critical safety issue which needed to be balanced by a clear benefit.

As already mentioned above liver function test abnormalities AESIs were reported at a higher incidence in the Combo 450 RP population than the Bini P population, overall (25.2% vs 17.3%), for Grade 3/4 AESIs (12.4% vs 4.2%) and for AESIs requiring dose adjustment/study drug interruption (8.4% vs 3%). Few events were serious (none vs 0.5%) or led to study drug discontinuation (1.8% vs 0.9%). In summary regarding liver function test abnormalities an additive effect of encorafenib und binimetinib can be suggested.

The data presented shows a high incidence of increases of GGT (overall and grade ¾) for the combination therapy. The mechanisms behind the GGT abnormalities are not understood. However, it seems to be a kind of class effect, for the MEK/BRAF inhibitor combinations.

Hepatic impairment

Liver metabolism mainly via glucuronidation is the primary route of elimination of binimetinib (see section 5.2). As encorafenib is not recommended in patients with moderate (Child Pugh B) and severe hepatic impairment (Child Pugh C), administration of binimetinib is not recommended in these patients (see sections 4.2 and 5.2).

Muscular toxicity:

Blood CK increase was a very commonly reported AE with binimetinib treatment (in 43.3% of patients treated at the recommended dose). This was rarely associated with symptoms, although symptoms were more common with higher reported grades of CK elevation. It was the most frequent cause of dose adjustment or treatment interruption. Frank rhabdomyolysis, defined by published criteria of high CK, evidence of end organ damage and muscle symptoms was infrequent, with only a single documented case meeting case defining criteria based on published literature and regulatory guidance. CK and creatinine levels should be monitored prior to initiating binimetinib, periodically during treatment, and as clinically indicated, and ensure that the patient is adequately hydrated. In case of rhabdomyolysis treatment should be discontinued. Depending on CK elevation, dose interruption or discontinuation of binimetinib may be required. Renal complications and clinical symptoms of myopathy are often clinically not very impressive, but their impact on overall morbidity and mortality should not be underestimated.

The addition of binimetinib to encorafenib appeared to mitigate the effects observed in the Bini P population.

Muscle-related AEs, including myalgia, have been observed with the administration of BRAF inhibitors including Encorafenib. The addition of binimetinib to encorafenib appeared to mitigate the effects observed in the Enco 300 mg population.

In summary, the combination therapy seems to mitigate both the incidence of elevations of the blood CK as well as the incidence of symptomatic myopathy, which makes the effect (as a MEKi class effect) per se more plausible.

The overall incidence of Muscle enzyme/protein changes AESIs was higher in the Combo 450 arm than in the vemurafenib arm overall. However, for the combination vemurafenib/cobimetinib a distinctly higher incidence of elevations of blood CK was seen (32.4% vemurafenib/cobimetinib vs 22.9% encorafenib/binimetinib).

See section 4.4 for further information on special warnings and precautions of use concerning CK elevation and rhabdomyolysis.

Left ventricular dysfunction:

This is a class effect of MEK. Left ventricular dysfunction occurred in 10% (44/427) of patients treated at the recommended dose, with a maximum severity of grade 3 (in 4.4% of patients). It frequently led to dose modification or treatment discontinuation. LVEF was routinely monitored with MUGA or echocardiography across the clinical program. The safety of binimetinib has not been established in patients with a baseline LVEF that is either below 50% or below the institutional lower limits of normal. It is recommended that there be assessment of LVEF by ECHO or MUGA scan before initiation of binimetinib, 1 month after initiation, and then at 2 to 3-month intervals while on treatment. Binimetinib should be interrupted for up to 3 weeks if absolute LVEF value decreases by 10% from pre-treatment values and is less than the lower limit of normal. Binimetinib should be permanently discontinued for symptomatic left ventricular dysfunction or persistent, asymptomatic left ventricular dysfunction that does not resolve within 3 weeks.

According the non-clinical data binimetinib has no electrophysiological effects in the heart and lack of effects on cardiac waveform and intervals (including QTc) at doses as high as 10 mg/kg (mean Maximum Concentration [Cmax] 2.7 µM, range 1.04 to 7.05 µM) in monkeys. QT prolongation was routinely monitored and classified as an AESI. This is confirmed by the clinical data in the different safety sets (restricted and broad). In the pivotal trial QTc prolongation events occurred with similar frequency in patients in both arms (binimetinib: 3.3% versus DTIC: 3.5%). All events were asymptomatic and none of the patients had presyncope, syncope or loss of consciousness associated with the QT prolongation, potentially indicating dangerous arrhythmias (e.g. “torsade de pointes”).

In the Combo 450 mg population the incidence of cardiac events overall and grade 3/4 were reported at a lower incidence in the Combo 450 RP population than in the Bini P population. In addition, there were no events leading to study drug discontinuation in the Combo 450 RP population whilst 4.2% were reported in the Bini P population. Few events were serious or required additional therapy. The most frequent PT in both populations was ejection fraction decreased (6.6% vs 10.3%). Compared to other MEK/BRAF inhibitor combinations events in the LVEF grouping were reported with a lower incidence in the encorafenib/binimetinib combination.

The recommendations in the SmPC (Section 4.2) regarding dose modifications (provided for cardiac adverse reactions, including asymptomatic, absolute decreases in LVEF from baseline of ≥ 10% and ejection fraction below the institutional LLN) currently is acceptable. See section 4.4 for further information on special warnings and precautions of use concerning left ventricular dysfunction.

Hypertension:

New-onset hypertension or worsening of hypertension was seen with binimetinib treatment in 16% (68/427) of patients at the recommended dose, with grade 3 in 8% of patients. It was generally manageable with antihypertensive medications and rarely required treatment discontinuation. Patients should be monitored for hypertension and temporary suspension of binimetinib is recommended in case of severe hypertension, until hypertension is controlled. The significantly high frequency for increases of creatinine (82.0%) indicating a decrease in renal function may explain at least partially this finding. It seems very likely that the increase in cardiac events was also triggered by hypertension results.

Hypertension is a class effect of MEK inhibitors, either when treated with these agents alone or in combination with a BRAF inhibitor (see also Mekinist® [trametinib] prescribing information; Cotellic® [cobimetinib] prescribing information). Hypertension AESIs were reported at a similar incidence in the Bini P and Combo 450 RP populations, overall (although the incidence was higher in the Bini P when adjusted for drug exposure) and for Grade 3/4 events (8.7% vs 6.2%).

In Study CMEK162B2301 Part 1, Kaplan-Meier plots of time to LVEF below 50% and/or absolute decrease of 10% or more in LVEF from baseline by baseline hypertension risk factor for patients in the Combo 450 arm with at least one event, showed a shorter median time for patients with as compared to patients without baseline hypertension risk factor. The incidence of a 2-grade shift in LVEF was higher in in the hypertension risk factor group (=history of hypertension, SBP ≥140 at screening, or DBP ≥ 90 at screening) as well.

The given recommendations regarding management and dose modifications in the SmPC section 4.2 as well as the warning in 4.4 are acceptable. See section 4.4 for further information on special warnings and precautions of use concerning hypertension.

Haemorrhage:

Although haemorrhage is classified as an AESI an occurred in 11.2 of patients in the binimetinib arm of the pivotal trial it seems that clinical relevant haemorrhage event beside epistaxis were not observed. The INR increases reported were also classified in this category, but no obvious reason for these elevations were found beside concomitant treatment with anticoagulants from the analyses. The PTs reported failed to indicate a clear signal for systemic impairment of haemostasis system or thrombocytes, although at the time being it cannot be completely excluded. The retinal haemorrhage (2.2% in the binimetinib arm) seems to reflect more a symptom of the retinal toxicity than really a bleeding disorder. Additionally, haematuria (0.4% in the binimetinib arm) in the absence of a haemostatic impairment is often symptom of a urogenital infection like acute cystitis. In summary, the data presented seemed not to indicate a significantly increase bleeding risk during binimetinib treatment.

Hemorrhages have been noted to occur with MEK-inhibitor treatment (see also Mekinist® [trametinib] prescribing information; Cotellic® [cobimetinib] prescribing information). Although the overall frequency of hemorrhage events was higher in the Combo 450 RP population as compared to the Bini P population, adjusting for exposure, the rate of hemorrhage events in the Combo 450 RP seems to be lower than the rate for the Bini P population. In comparison with the other known BRAF/MEK inhibitor combination therapies the overall incidence of a hemorrhage seems to be similar. However, the incidence of Grade ¾ events is higher under the combination therapy with encorafenib and binimetinib compared to the other combinations. Preliminary data of part 2 of the pivotal study indicates a slightly reduced incidence in the Combo 300 mg population.

See section 4.4 for further information on special warnings and precautions of use concerning haemorrhage.

Pneumonitis:

This was seen following binimetinib treatment in 1.4% of patients in the all cancers [binimetinib any dose] population) and is a well-recognized ADR associated with a number of kinase inhibitors, including MEK inhibitors. The underlying mechanism behind pulmonary toxicities, considered as being MEK inhibitor class effects, is not yet known. It has been hypothesized that the blockage of epidermal growth factor receptor (EGFR)-dependent epithelial proliferation by EGFR tyrosine kinase inhibitors augments pulmonary fibrosis (Min et al, 2011, Suzuki et al, 2003). However, it is notable that MEK inhibition may not have the same effect. For example, an *in vivo* study in mice demonstrated that the MEK inhibitor, selumetinib (ARRY-142886), prevented the progression of established pulmonary fibrosis associated with EGFR activation (Madala et al 2012).

Pneumonitis/interstitial lung disease (ILD) has been noted to occur with MEK-inhibitor treatment (Mekinist® [trametinib] prescribing information; Cotellic® [cobimetinib] prescribing information), including binimetinib. Pneumonitis AESIs were reported at a similar (low) overall incidence in the Bini P and Combo 450 RP populations.

See section 4.4 for further information on special warnings and precautions of use concerning pneumonitis/ILD.

Renal Failure:

The incidence of renal failures seems to be similar in the presented safety populations. However, the severity seems to be higher in the combo 450 populations than in the binimetinib and encorafenib mono populations (higher incidence of grade ¾ events and SAEs).

Gastro-intestinal disorders

Including diarrhoea and vomiting: in the 9-month repeat-dosing study in the monkey, the primary findings were gastrointestinal intolerance and inflammation. All large intestinal findings resolved after a treatment-free period. In the gastric irritation study in rats, there were no significant effects at the 10 and 30 mg/kg doses. At 100 mg/kg binimetinib, there was an increased incidence of superficial mucosal lesions and of haemorrhagic ulcers. ADRs reported most commonly by PT at the recommended dose were diarrhoea (43% of patients), nausea (30% of patients) and vomiting (20% of patients). Gastrointestinal events required dose adjustment or study drug interruption in 11% of patients and led to discontinuation of binimetinib in 1.2% of patients.

Regarding preliminary data of part 2 of the pivotal incidences seem to be remarkably higher in the Combo 450mg than in the Combo 300mg population. In addition, the incidence of abdominal pain was remarkably higher compared to other MEK/BRAF inhibitors.

Pancreatitis is a known effect of BRAF inhibitors (Muluneh et al. 2013). Although in most cases the increase of lipase and amylase in the Combo 450mg RP was asymptomatic and the incidence of acute pancreatitis was low, it seems to be an important safety issue. The incidence is comparable with that reported for marketed BRAF inhibitors, and the ADR attribution is also comparable. Based on the available data, this identified risk is not considered a safety concern in the updated encorafenib RMP in the context of the severity of metastatic disease. Lipase increased and amylase increased are both reported as common ADRs (<10%).

The common ADRs in the category of gastrointestinal disorders include nausea, diarrhoea, vomiting, abdominal pain and constipation. In the Combo 450 arm of the pivotal study AEs in this category were reported overall in 71.9% including Grade 3/4 events in 11.9% and SAEs in 9.4%. 42.2% % of the patients needed additional therapy. Incidences seem to be remarkably higher in the Combo 450mg than in the Combo 300mg population (71.9% vs 63.8%, preliminary data of part 2 of the pivotal study). In addition, the incidence of abdominal pain was remarkably higher compared to other MEK/BRAF inhibitor combinations. The given information in the SmPC for binimetinob is acceptable.

Anaemia:

Occurred in 18.2% of patients in the Combo 450 RP population (vs 9.6% in the Bini P population), 4.4% patients had grade 3/4 events (vs 2.3% in the Bini P population). No patients discontinued Combo 450 RP due to anaemia, 1.5% required dose adjustment or study drug interruption and 9.5% patients required additional therapy. With regard to the preliminary data, incidences were remarkably higher in the Combo 450mg arm (Part 1) than in the Combo 300mg arm (Part 2) of the pivotal study (15.1% vs 9.3%). Compared to other MEK/BRAF inhibitors, a higher incidence of grade 3/4 anaemia was reported with the combination therapy binimetinib/encorafenib than with other combinations.

Venous thromboembolism:

In melanoma patients treated at the recommended dose of binimetinib, VTE occurred in 4.2% (18/427) of patients receiving binimetinib, including 1.4% (6/427) of patients with pulmonary embolism. It is a common complication related to malignancy and there is generally a high degree of vigilance for signs and symptoms of VTE in cancer patients, and use of thromboprophylaxis in appropriate settings is recognized as a standard of care in oncology.

See section 4.4 for further information on special warnings and precautions of use concerning venous thromboembolism.

Reproductive risk:

Based on findings from animal studies and its mechanism of action, binimetinib may cause foetal harm when administered to a pregnant woman. Binimetinib was embryotoxic and abortifacient in rabbits at

doses greater than or equal to those resulting in exposures approximately 12 times the human exposure at the recommended clinical dose. The main risk factor is the women of child-bearing potential (i.e., pre or peri-menopausal) with exposure during the first trimester without effective method of contraception. The risk may be managed by highlighting in the patient information leaflet/summary of product characteristics that female patients of reproductive potential should use effective contraception during treatment with binimetinib and for 2 weeks after treatment.

There are no data on the effect on fertility in humans for binimetinib.

The overall incidence of SAEs and of SAEs of Grade 3 / 4 was similar in the Bini P and Combo 450 RP populations. However the onset of SAEs was earlier for binimetinib monotherapy (1.6 month) than for the combination binimetinib/encorafenib (3.8 months in the Combo 450 RP population resp 3.5 months in the Combo 450 arm of the pivotal study). In addition, in contrast to binimetinib monotherapy, SAEs were reported (in low incidences) for several different PTs and not particular for the PT general physical health deterioration (possibly due to the multiplicity of toxicities).

In Study CMEK162B2301 Part 1, a similar percentage of patients died on treatment across the three treatment arms (8.9% Combo 450 arm, 7.3% encorafenib Part 1 arm, 10.2% vemurafenib arm). The adjusted death rate per 100 patient-months of exposure was 0.71 in the Combo 450 arm, 0.75 in the encorafenib Part 1 arm and 1.23 in the vemurafenib arm. In the Binimetinib monotherapy population the incidence seems to be similar as well. However, the adjusted death rate was higher (2.45) indicating in a shorter survival of this monotherapy population.

Binimetinib is a substrate of UGT1A1. It is suggested that a study with an inhibitor is not required but instead cautionary wording is proposed. This is not agreed. Data on the effect of polymorphisms is limited and there are few patients on UGT inhibitors in the POPPK analysis (n=20) and this is not as sensitive to determine an effect. The applicant should perform a study to determine the effect of UGT1A1 inhibitors on binimetinib.

Binimetinib is also a substrate for Pgp and BCRP, however an effect on biliary secretion is proposed to be unlikely based on non-clinical data and effects on absorption unlikely, due to high intestinal permeability. This too is not accepted and it is considered a clinical study should be performed to determine the effect of Pgp and BCRP inhibition.

In cocktail uptake studies binimetinib did not appear to be a substrate of hepatic uptake transporters. The concentration studied however is high, 15.3 µM compared to Cmax,u of 0.06µM, further studies are required at more physiologically relevant concentrations.

Binimetinib does not inhibit CYPs except for CYP 2B6 which had a Ki of 1.7 µM, however the mechanistic static model was used to rule out an interaction.

Binimetinib shows induction of CYP 3A4 in vitro and this was investigated in a clinical study. Induction of mRNA for CYP 1A2 and 2B6 is greater than 2-fold (16.5 and 2.6-fold respectively). This should be discussed.

Binimetinib is not an inhibitor of Pgp, BCRP, OAT1, OCT1, OCT2, MATE-1, MATE-2k or BSEP. It is a weak inhibitor of OATP1B1 and 1B3, but it can be agreed this does not appear to be at clinically relevant concentrations and therefore there are no safety concerns. Binimetinib does inhibit OAT3 and further clarification should be provided to discount an effect on this transporter.

Non-cutaneous malignancies

Based on its mechanism of action, encorafenib may promote malignancies associated with activation of RAS through mutation or other mechanisms. Patients receiving binimetinib in combination with

encorafenib should undergo a head and neck examination, chest/abdomen computerised tomography (CT) scan, anal and pelvic examinations (for women) and complete blood cell counts prior to initiation, during and at the end of treatment as clinically appropriate.
Permanent discontinuation of binimetinib and encorafenib should be considered in patients who develops RAS mutation-positive non-cutaneous malignancies. Benefits and risks should be carefully considered before administering binimetinib in combination with encorafenib to patients with a prior or concurrent cancer associated with RAS mutation.

Lactose intolerance

Mektovi contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Contraindications: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Overdose

The highest dose of binimetinib evaluated as single agent in clinical studies was 80 mg administered orally twice daily and was associated with ocular (chorioretinopathy) and skin toxicities (dermatitis acneiform).

There is no specific treatment of overdose. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

Since binimetinib is highly bound to plasma proteins, haemodialysis is likely to be ineffective in the treatment of overdose with binimetinib.

Elderly

In patients treated with Combo 450 (n = 274), 194 patients (70.8 %) were < 65 years old, 65 patients (23.7 %) were 65 -74 years old and 15 patients (5.5 %) were aged > 75. No overall differences in safety or efficacy were observed between elderly patients (≥ 65) and younger patients. The proportion of patients experiencing adverse events and serious adverse events were similar in patients aged <65 years and those aged ≥ 65 years. The most common adverse events reported with a higher incidence in patients aged ≥ 65 years compared to patients aged < 65 years included diarrhoea, pruritus, GGT and blood phosphatase alkaline elevation. In the small group of patients aged ≥ 75 years (n=15), patients were more likely to experience serious adverse events and adverse events leading to discontinuation of treatment.

Binimetinib has minor influence on the ability to drive or use machines. Visual disturbances have been reported in patients treated with binimetinib during clinical trials. Patients should be advised not to drive or use machines if they experience visual disturbances or any other adverse reaction that may affect their ability to drive and use machines (see sections 4.4 and 4.8).

Dose modification

The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation (see section 4.2 and Table 1 and Table 2 of the SmPC).

For patients receiving 45 mg binimetinib twice daily, the recommended reduced dose of binimetinib is 30 mg twice daily. Dose reduction below 30 mg twice daily is not recommended. Therapy should be discontinued if the patient is not able to tolerate 30 mg orally twice daily.

If the adverse reaction that resulted in a dose reduction is under effective management, dose re escalation to 45 mg twice daily may be considered. Dose re escalation to 45 mg twice daily is not recommended if the dose reduction is due to left ventricular dysfunction (LVD) or any Grade 4 toxicity.

If treatment related toxicities occur when binimetinib is used in combination with encorafenib, then both treatments should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose reductions are necessary for encorafenib only (adverse reactions primarily related to encorafenib) are: palmar-plantar erythrodysaesthesia syndrome (PPES), uveitis including iritis and iridocyclitis and QTc prolongation.

If binimetinib is temporarily interrupted, encorafenib should be reduced to 300 mg once daily during the time of binimetinib dose interruption (see Tables 1 and 2) as encorafenib is not well-tolerated at the dose of 450 mg as a single agent. If binimetinib is permanently discontinued, encorafenib should be discontinued.

If encorafenib is temporarily interrupted (see section 4.2 of encorafenib SmPC), binimetinib should be interrupted. If encorafenib is permanently discontinued, then binimetinib should be discontinued.

For information on the posology and recommended dose modifications of encorafenib, see section 4.2 of encorafenib SmPC.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

2.6.2. Conclusions on the clinical safety

The overall safety results for binimetinib show ADRs consistent with the known safety profile of other drugs in this class and are considered acceptbale and manageable with routine risk minimisation activities. However, the incidences of some of the expected adverse events are more frequent that seen with other approved MEK inhibitors. Some of these ADRs are serious or potentially life threatening (thromboembolic events, hypertension, serious skin toxicities and infections, left ventricular dysfunction, pneumonitis, liver function abnormalities and rhabdomyolysis), or are sight threatening (RVO) and are reflected in the deaths, SAEs and AEs leading to discontinuation across the safety sets.

The safety and tolerability of binimetinib in combination with encorafenib appears favourable and acceptable as compared to vemurafenib with regard to the observed benefit. The majority of the reported ADRs reflects the common AEs observed in the clinical program of binimetinib 45 mg QD single agent and given in combination to binimetinib 45 mg BID. The observed toxicities of the combination are generally manageable and acceptable in the population of adult patient with metastatic or unresectable melanoma harbouring a BRAFV600 mutation, and no prior therapy. The overall safety profile of the combination of binimetinib 45 mg BID with encorafenib 450 mg QD is consistent with the mechanisms of action and the known safety profiles of MEK and BRAF inhibitors as single agents or in combination.

A comparison of safety profile between Combo 450 and Combo 300 suggests a better safety profile with the Combo 300 with lower incidences of grade 3-4 events and serious adverse events. The overall safety profiles for the Combo 450 and Combo 300 arms are similar in terms of incidence (difference<5%) of deaths, AEs, treatment discontinuation due to AEs, and AEs leading to dose

modifications/ interruptions or additional therapy. The overall incidence of grade 3-4 AEs was lower in the Combo°300 (46.7% vs 57.8%) as compared to Combo 450.

A 4-month update of the safety profile was provided with the responses. The updated safety data provided with additional follow-up shows a similar safety profile for the Combo 450 as demonstrated in the initial submission. New ADRs of blood creatinine increased, renal failure and GGT increased for encorafenib in combination with binimetinib, and blood creatinine increased for encorafenib single agent, have been added to the proposed SmPC since the initial submission.

2.7. Risk Management Plan

Safety concerns

Safety concerns of binimetinib in combination with encorafenib
Important identified risks
- Left ventricular dysfunction - Hypertension - Rhabdomyolysis - Retinal pigment epithelial detachment - Venous thromboembolism - Haemorrhage
Important potential risks
- Hepatotoxicity - Pneumonitis/Interstitial lung disease - Retinal vein occlusion - Embryo-foetal toxicity - Over-exposure in patients with moderate to severe hepatic impairment
Missing information
- Use in patients with reduced cardiac function (LVEF <50%) or symptomatic chronic heart failure

Pharmacovigilance plan

There is no planned or ongoing additional study in the pharmacovigilance plan.

Routine pharmacovigilance activities are sufficient to address the safety concerns of this medicinal product.

Risk minimisation measures

Safety Concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important identified risks for binimetinib in combination with encorafenib		
Left ventricular dysfunction	Routine: Dose modification recommendations in Section 4.2 of the	Routine Additional: none.

Safety Concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC. Warning in Section 4.4 of the SmPC and relevant PIL section. Listed in Section 4.8 of the SmPC and relevant PIL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products. Additional: none.	
Hypertension	Routine: Dose modification recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PIL section. Listed in Section 4.8 of the SmPC and relevant PIL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products. Additional: none.	Routine Additional: none.
Rhabdomyolysis	Routine: Dose modification recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PIL section. Listed in Section 4.8 of the SmPC and relevant PIL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products. Additional: none.	Routine Additional: none
Retinal pigment epithelial detachment (RPED)	Routine: Dose modification recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PIL section. Listed in Section 4.8 of the SmPC and relevant PIL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products. Additional: none.	Routine Additional: none.

Safety Concern	Risk minimisation measures	Pharmacovigilance activities
Venous thromboembolism (VTE)	Routine: Dose modification recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PIL section. Listed in Section 4.8 of the SmPC and relevant PIL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products. Additional: none.	Routine Additional: none.
Haemorrhage	Routine: Dose modification recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PIL section. Listed in Section 4.8 of the SmPC and relevant PIL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products. Additional: none.	Routine Additional: none.
Important potential risks for binimetinib in combination with encorafenib		
Hepatotoxicity	Routine: Dose modification recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PIL section. Listed in Section 4.8 of the SmPC and relevant PIL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products. Additional: none.	Routine Additional: none
Pneumonitis/ Interstitial lung disease	Routine: Dose modification recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PIL section. Listed in Section 4.8 of the SmPC and relevant PIL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products. Additional: none.	Routine Additional: none
Retinal vein	Routine:	Routine

Safety Concern	Risk minimisation measures	Pharmacovigilance activities
occlusion (RVO)	Treatment discontinuation is recommended in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PIL section. Listed in Section 4.8 of the SmPC and relevant PIL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products. Additional: none.	Additional: none
Embryo-foetal toxicity	Routine: Warning in Section 4.6 of the SmPC and relevant PIL section. Information provided in Section 5.3 of the SmPC. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products. Additional: none.	Routine Additional: none.
Over-exposure in patients with moderate to severe hepatic impairment	Routine: Reduced dose and dose modification recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PIL section. Information in Section 5.2 of the SmPC. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products. Additional: none	Routine Additional: none.
Missing information for binimetinib in combination with encorafenib		
Use in patients with reduced cardiac function (<50%) or symptomatic chronic cardiac failure	Routine: Warning in Section 4.4 of the SmPC and relevant PIL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products. Additional: none.	Routine: Additional: none.

Routine risk minimisation measures are considered sufficient to minimise the safety concerns of this medicinal product.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.7 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 27 June 2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of binimetinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers binimetinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Mektovi (binimetinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applicant applied for a marketing authorisation application for an indication of binimetinib for use in combination with encorafenib for the treatment of adult patients with unresectable or metastatic melanoma, with BRAF V600 mutation.

3.1.2. Available therapies and unmet medical need

BRAF- MEK inhibitor combination regimens are currently the main standard of care for treatment of advanced unresectable or metastatic melanoma that have tumours harbouring the BRAF V600 mutation. Tumour responses have reported as high as up to 70% and rapid response induction has been associated with symptom control. Median PFS has been shown to be increased to approximately 12 months and this has translated into an improvement in median OS to 22-25 months.

Other treatment options include anti PD-1 antibodies, nivolumab and pembrolizumab, which showed a clinically and statistically significant PFS benefit over the anti-CTLA4 antibody ipilimumab. Emerging data suggest that BRAF inhibition is effective following immunotherapy, and checkpoint inhibitors are still effective in patients who have progressed on kinase-inhibitor therapy.

Although there are treatments for metastatic melanoma with BRAFV600 mutation that have shown clinical benefit, patients usually relapse or discontinue due to AE or tolerability issues. Therefore, there is still a need for treatment choices with improved efficacy or different safety profiles over existing medicinal products.

3.1.3. Main clinical studies

The Phase 3 clinical study (COLUMBUS) was a randomised, open label trial in patients with advanced unresectable or metastatic BRAF (either V600 E or K) mutation-positive melanoma comprised of 2 parts:

- Part 1 randomised 577 patients in a 1:1:1 ratio to encorafenib 450mg QD and binimetinib 45mg BID (Combo 450, N=192), encorafenib 300mg QD (N=194) or vemurafenib 960mg BID (N=191). Randomisation was stratified by AJCC stage, ECOG performance status and prior first line immunotherapy.
- Part 2 was planned to randomise 320 patients in a 3: 1 ratio to Combo 300 (encorafenib 300mg QD and binimetinib 45mg BID) or encorafenib 300mg QD. This part of the trial was to estimate the treatment effect of Combo 300 vs. LGX818 in terms of overall survival (OS), to estimate the treatment effect of Combo 300 vs. vemurafenib in terms of PFS and OS and to estimate the treatment effect of Combo 300 vs. Combo 450 in terms of PFS and OS.

3.2. Favourable effects

The DMC advised study termination on 14 October 2016 based on unblinded efficacy data, including OS results to which the Sponsor remained blinded. The Part 1 efficacy data were presented in the initial dossier and the Part 2 results were provided during the procedure.

The trial met its primary endpoint, with an improved median PFS by 7.6 months in the Combo 450 arm compared to single agent vemurafenib with a median PFS of 14.9 months vs. 7.3 months, respectively, HR = 0.54 (95% CI 0.41, 0.71, 1 -sided stratified log-rank p<0.001) is the FAS.

The HR was consistent by investigator review and in the sensitivity analyses, including an analysis counting new therapy as an event (HR=0.53).

The median PFS of single agent vemurafenib (7.3 months) was consistent with what has been seen in previous studies and, it was noted that the median PFS of the Combo 450 (14.9 months) was longer than that reported for other BRAF- MEK inhibitor combination treatments (median PFS for trametinib and dabrafenib = 11.4 months; cobimetinib and vemurafenib = 12.3 months).

Encorafenib monotherapy increased median PFS by 2.3 months compared to vemurafenib (9.6 months vs. 7.3 months; nominal one-sided log-rank p = 0.004; HR = 0.68, 95% CI 0.52, 0.90) by BIRC. This was a secondary efficacy endpoint, downgraded from a co-primary endpoint with Protocol Amendment 3 (post randomisation of 364 patients). Investigator assessment of response gave similar median PFS durations. Median PFS values by BIRC were the same in the PPS as in the FAS.

The confirmed overall response rate (ORR) per BIRC was higher with combination treatment: 63.0% (95% CI 55.8, 69.9) in the Combo 450 arm compared with 50.5% (95% CI 43.3, 57.8) in the encorafenib arm and 40.3% (95% CI 33.3, 47.6) in the vemurafenib arm.

The median time to definitive 10% deterioration in the FACT-M global health status score was not reached in the Combo 450 arm (95% CI 22.1, NE) and was 22.1 months (95% CI 15.2, NE) in the vemurafenib arm with a HR for the difference of 0.46 (95% CI 0.29, 0.72) using a stratified Cox regression model. The median time to definitive 10% deterioration in the FACT-M was 20.3 months (95% CI 15.0, NE) in the encorafenib arm with a HR for the difference between Combo 450 and encorafenib of 0.48 (95% CI 0.31, 0.75) using a stratified Cox regression model.

The median time to definitive 10% deterioration in the EORTC QLQ-C30 global health status score was delayed by 7.3 months in the Combo 450 arm compared to the vemurafenib arm: 23.9 months (95% CI 20.4, NE) vs. 16.6 months (95% CI 11.9, NE) with a HR for the difference of 0.55 (95% CI 0.37, 0.80) using a stratified Cox regression model. The median time to definitive 10% deterioration in the QLQ-C30 global health status scores was 9.2 months longer in the Combo 450 arm compared with the Enco 300 arm (14.7 months [95% CI 9.2, 18.4]), with a HR for the difference of 0.45 (95% CI 0.31, 0.65) using a stratified Cox regression model.

The median OS was 33.6 months (95% CI [24.4, 39.2]) and 16.9 months ((95% CI [14.0, 24.5]) for Combo 450 compared to vemurafenib (HR 0.61, 95% CI 0.47, 0.79, nominal p value <0.0001). Estimates of OS at 12 months and 24 months were 75.5% (95% CI [68.8, 81.0]) and 57.6% ((95% CI [50.3, 64.3]) for Combo 450 compared to 63.1% ((95% CI [55.7, 69.6]) and 43.2% ((95% CI [35.9, 50.2]) for vemurafenib.

The median (95% CI) OS was 33.6 months (24.4, 39.2) and 23.5 months (19.6, 33.6) with Combo 450 compared to encorafenib, respectively, with a HR 0.81 (95% CI 0.61, 1.0; nominal p value =0.0613, 2-sided). Estimates of OS at 12 months and 24 months were 75.5% (68.8, 81.0) and 57.6% (50.3, 64.3) for Combo 450 compared to 74.6% (67.6, 80.3) and 49.1% (41.5, 56.2) for encorafenib.

3.3. Uncertainties and limitations about favourable effects

There were some uncertainties concerning the best dose for encorafenib (450mg vs 300 mg) that should be used in combination with binimetinib. Single agent binimetinib has limited activity in BRAF-mutated melanoma patients. In the phase II study CMEK162X2201, the 4.9% response rate in 41 patients, based on locally assessed unconfirmed responses, is low for a monotherapy MEK inhibitor compared to results of trametinib reported in a pivotal phase III study. Binimetinib 45mg BID contributed to the efficacy of Combo 300 and allowed a higher dose of encorafenib to be administered in Combo 450.

It was unclear whether Combo 450 offered an additional PFS benefit over Combo 300. In the analysis with comparable median duration of potential follow-up for PFS (16.7 months and 13.9 months), Combo 450 showed a median 2-month improvement in PFS compared with Combo 300 (14.9 vs 12.9 months). This difference was not statistically significant (HR of 0.79 [95% CI 0.60, 1.03]) one-sided log-rank p=0.0845). The second analysis performed using the 09 November 2016 cut-off date for the two arms was statistically significant (HR 0.73 95%CI [0.55 0.97]; 2-sided p=0.0278). However, this

result is due to a very uneven duration of follow-up for PFS per BIRC (Kaplan Meier) with 22.5 months for Part 1 Combo 450 arm compared with 13.9 months for Part 2 Combo 300 arm. Combo 450 did not improve the response rate compared with Combo 300 (63.0% vs 65.9%) but did lead to a numerically longer duration of confirmed responses (16.6 months vs 12.7 months).

Normally statistical significance would not be demanded between the two parts of the study and the 2.8-month improvement in median PFS with Combo 450 compared with Combo 300 could be considered clinically relevant. However, in this instance, the fact that encorafenib 300mg performed significantly better in Part 1 than in Part 2 with a 2.2-month difference in median PFS hinders the PFS comparison of the combination treatment (Combo 450 vs Combo 300) between the two parts of the study. Therefore, the OS results for Combo 300 and updated Combo 300 PFS analysis, including more mature data for the Enco300 Part 2 arm will be provide as a post-authorisation measure.

The Exposure-Response analyses suggest that increasing encorafenib AUC_{ss} in Combo 450 has a negative influence on ORR and PFS. Baseline LDH >ULN was more common in patients with a higher AUC_{ss}; high LDH is known to be a negative prognostic marker predicting a shorter PFS. In Part 1, in the high LDH group only patients with high encorafenib exposure in Combo 450 did worse. There was no such finding with Combo 300 in Part 2. There remains the possibility that this association in the Combo 450 arm is a chance finding or artefact. It remains possible that the B/R ratio could be improved in patients with high baseline LDH by identification of other factors that potentially influence encorafenib exposure. Therefore, the applicant is requested to submit the overall survival results stratified by LDH level for Combo 300 and Enco 300 (Part 2) as a post-authorisation measure.

In order to characterise the patient population that responds to treatment, the applicant is requested to submit the results of the planned biomarker analyses for Study B2301 (from all 3 treatment arms) for evaluation as soon as available, to support the synergistic pharmacodynamic activity of encorafenib in combination with binimetinib. The results will be provided as a recommendation.

In addition, genomic analysis of baseline samples remaining after centralized BRAF testing would be informative to assess whether there is a relationship between baseline mutations and efficacy outcomes. As indicated in the protocol, genomic alterations in BRAF, HRAS, KRAS, NRAS, PTEN, cKIT, PIK3CA, MAP2K1, MAP2K2, ARAF, c-MET, CRAF, EGFR and CCND1 may be explored to find a potential association between baseline mutations and efficacy outcomes. The results will be provided as a recommendation.

3.4. Unfavourable effects

The safety of binimetinib (45 mg orally twice daily) in combination with encorafenib (450 mg orally once daily) (hereafter referred to as Combo 450) was evaluated in 274 patients with BRAF V600 mutant unresectable or metastatic melanoma, based on two Phase II studies (CMEK162X2110 and CLGX818X2109) and one Phase III study (CMEK162B2301, Part 1) (hereafter referred to as the pooled Combo 450 population). At the recommended dose (n = 274) in patients with unresectable or metastatic melanoma, the most common adverse reactions (> 25 %) occurring in patients treated with binimetinib administered with encorafenib were fatigue, nausea, diarrhoea, vomiting, retinal detachment, abdominal pain, arthralgia, blood CK increased and myalgia.

The safety of encorafenib (300 mg orally once daily) in combination with binimetinib (45 mg orally twice daily) was evaluated in 257 patients with BRAF V600 mutant unresectable or metastatic melanoma (hereafter referred to as the Combo 300 population), based on the Phase III study (CMEK162B2301, Part 2). The most common adverse reactions ($\geq$25%) occurring in patients treated with encorafenib 300 mg administered with binimetinib were fatigue, nausea and diarrhoea.

The overall safety results for binimetinib show ADRs consistent with the known safety profile of other drugs in this class. However, the incidences of some of the expected adverse events are more frequent that seen with other approved MEK inhibitors. Some of these ADRs are serious or potentially life threatening (thromboembolic events, hypertension, serious skin toxicities and infections, left ventricular dysfunction, pneumonitis, liver function abnormalities and rhabdomyolysis), or are sight threatening (RVO) and are reflected in the deaths, SAEs and AEs leading to discontinuation across the safety sets.

The safety and tolerability of binimetinib in combination with encorafenib appears favourable and acceptable as compared to vemurafenib regarding the observed benefit. The majority of the reported ADRs reflects the common AEs observed in the clinical program of binimetinib 45 mg QD single agent and given in combination to binimetinib 45 mg BID. Regarding the presented safety data of part 2, Combo 300 seems to be better tolerable than Combo 450.

Pneumonitis is an important potential risk. This was seen following binimetinib treatment in 1.4% of patients in the all cancers [binimetinib any dose] population) and is a well-recognized ADR associated with a number of kinase inhibitors, including MEK inhibitors. T

Specifically, for binimetinib, the most important risks associated with binimetinib treatment defined by ADRs in the proposed patient population are (see warning in SmPC 4.4):

- Left ventricular dysfunction: is a class effect of MEK. Left ventricular dysfunction occurred in 10% (44/427) of patients treated at the recommended dose, with a maximum severity of grade 3 (in 4.4% of patients). It frequently led to dose modification or treatment discontinuation. LVEF was routinely monitored with MUGA or echocardiography across the clinical program.
- Hypertension: New-onset hypertension or worsening of hypertension was seen with binimetinib treatment in 16% (68/427) of patients at the recommended dose, with grade 3 in 8% of patients. It was generally manageable with antihypertensive medications and rarely required treatment discontinuation.
- RPED and RVO: the ocular toxicities of binimetinib can be sight threatening although no cases of permanent blindness have been reported. Visual impairment, including vision blurred and reduced visual acuity, occurred in 13% (56/427) of patients and was generally reversible. RPED is a characteristic adverse effect of MEK. RVO was seen infrequently (1.6% [9/566 patients in the all cancers (binimetinib any dose) population]), but is a potentially sight-threatening event.
- Muscular toxicity with a blood CK increase was a very commonly reported AE with binimetinib treatment (in 43.3% of patients treated at the recommended dose). Frank rhabdomyolysis, defined by published criteria of high CK, evidence of end organ damage and muscle symptoms was infrequent, with only a single documented case meeting case defining criteria based on published literature and regulatory guidance. CK and creatinine levels should be monitored prior to initiating binimetinib, periodically during treatment, and as clinically indicated, and ensure that the patient is adequately hydrated. The incidence of musculoskeletal toxicity was higher in the use in combination with encorafenib.
- Haemorrhagic events were observed in 17.9 % (49/274) of patients in the pooled Combo 450 population. Most of these cases were Grade 1 or 2 (14.6 %) and 3.3 % were Grade 3 or 4 events. Few patients requiring dose interruptions or dose reductions (0.7 % or 2/274).

- VTE occurred in 4.7 % (13/274) in patients treated with Combo 450, including 2.2 % (6/274) of patients who developed pulmonary embolism.

The overall tolerability profiles of Combo 450 and Combo 300 were broadly similar in terms of AEs requiring discontinuation, dose modifications or additional therapy but Combo 450 led to increased incidence of SAEs and Grade 3-4 AEs. Combo 450 generated an increased incidence of the most common side effects compared to Combo 300, particularly nausea (41.1 vs. 27.2%), vomiting (29.7 vs. 15.2) and headache (21.9 vs. 11.7%). The time to first SAE and AE resulting in study drug discontinuation was shorter for Combo 450.

3.5. Uncertainties and limitations about unfavourable effects

There is the potential risk of embryo-foetal toxicity as described in the non-clinical section. This potential risk has been communicated in the SmPC in section 4.6. There is also a potential risk of over-exposure of binimetinib in patients with moderate to severe hepatic impairment. The potential hs been described in the SmPC and recommendations for dose modification has been added to section 4.2 of the SmPC.

Missing information regarding safety includes information regarding use in patients with reduced cardiac function (LVEF <50%) or symptomatic chronic heart failure and safety in paediatric population (children less than 18 years) (see RMP).

There is a potential of over-exposure in patients with moderate to severe hepatic impairment. The CHMP considers that the applicant should collect PK samples from BRAF melanoma patients with moderate and severe hepatic impairment after repeated dosing of encorafenib in combination with binimetinib to determine the plasma concentrations in relation to administered dose and AEs observed to guide dosing recommendations in these patient populations.

3.6. Effects Table

Table 83. Effects Table for Binimetinib in Combination with Encorafenib for the Treatment of Adult Patients with Unresectable or Metastatic Melanoma with BRAF V600 mutation (data cut-off: 19 May 2016).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Median PFS	Combo 450 vs Vem	months	14.9	7.3	Strong; consistent across analyses + previous BRAF-MEKi combos; uncertainty re binimetinib contribution	
Median PFS	Enco vs. Vem	months	9.6	7.3	Strong; little uncertainty	
Median PFS	Combo 450 vs Enco	months	14.9	9.6	HR: 0.77 (95% CI [0.59-1]), one sided nominal p value=0.0249	
Overall survival OS	Combo 450 vs Vem	months	33.6	16.9	Stratified Hazard Ratio: 0.6195% CI: (0.47, 0.79)Log-rank p-value: <0.0001TreatmentCombo	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Overall survival OS	Combo 450 vs Enco	months	33.6	23.5	HR 0.81, 95% CI 0.61, 1.06, nominal p value =0.0613, 2-sided	

Unfavourable Effects – initial MAA (except deaths updated 9 November 2016)

		Combo 450 RP	Enco 300 P	Vem	
EAIR All grade AEs	Per 100 patient-months	142.83	604.83	226.32	
G3/4 AEs	Treatment emergent %	58.0	67.3	63.4	
SAEs	Treatment emergent %	35.8	31.8	37.1	
Dis-contin	Treatment emergent %	10.2	17.5	16.7	
G3/4 PPE	Treatment emergent %	0.0	12.4	1.1	
G3/4 vomiting	Treatment emergent %	2.2	4.1	1.6	
G3/4 diarrhoea	Treatment emergent %	3.3	1.4	2.2	
G3/4 inc. CK	Treatment emergent %	5.5	0.0	0.0	
G3/4 inc GGT	Treatment emergent %	8.0	4.6	3.2	
G3/4 inc transamin	Treatment emergent %	5.8	1.4	1.6	
G3/4 haemorrhage	Treatment emergent %	2.6	1.8	1.0	
SCC	Treatment emergent %	2.6	6.9	17.2	
On treatment deaths	%	10.2	7.4	10.2	
EAIR deaths	Per 100 patient-months	0.73	0.71		

Abbreviations: Combo 450: encorafenib 450mg QD + binimetinib 45mg BID; Enco: encorafenib 300mg QD; Vem: vemurafenib 960mg BID; mon: months; EAIR: exposure adjusted incidence rate; G: Grade; AE: adverse event; Dis-contin: discontinuation due to AE; transamin: transaminases; inc: increased; HTN: hypertension; SCC: squamous cell carcinoma; aPPE: -Palmar-plantar erythrodysaesthesia syndrome

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The PFS improvement for Combo 450 compared to vemurafenib is considered clinically meaningful. In addition, the significant prolongation in OS with a difference in median survival of 16.7 months in favour of Combo 450 is clinically important.

Combo 450 had better general tolerability than encorafenib monotherapy, as evidenced by the QoL analysis and the lower overall rate of AEs. Treatment continued at high relative dose intensity in the combination arm. Still, the proportion of SAEs was not reduced compared to encorafenib monotherapy, and the combination did introduce additional toxicities, specifically increased CK, hypertension, abnormal LFTs, LV dysfunction and eye disorders. These events may not have influenced tolerability, but decreased ejection fraction and increased ALT did result in dose adjustment or study drug interruption. These AEs have the potential to be serious but are manageable if the routine regular screening of patients whilst on treatment is adhered to and recommendations from the SmPC are followed.

3.7.2. Balance of benefits and risks

BRAF-MEK inhibitor combinations are known to be effective in BRAF V600 mutant malignant melanoma. Combo 450 led to an improved PFS compared to monotherapy vemurafenib and a median OS at the upper end of the range of survivals currently reported for metastatic malignant melanoma. While vemurafenib monotherapy is no longer the main standard of care for metastatic melanoma with BRAF V600 mutations and as a result, the comparison with a treatment arm which is currently regarded as suboptimal is not encouraged, it nevertheless remains evident that there is a clinically relevant benefit that has been demonstrated with the combination treatment of encorafenib with binimetinb in patients with metastatic melanoma harbouring BRAF V600 mutation. The safety of the combination is considered acceptable and ADRs can be managed through routine risk minimisation activities with no further additional risk minimisation activities required.

3.7.3. Additional considerations on the benefit-risk balance

Approximately 37-50% of patients with metastatic melanoma have mutations in *BRAF*, and over 95% of these are in *BRAF* exon 15 at the V600 position. The most common V600 mutations are V600E and V600K accounting for 80-90% and 7-30% of all *BRAF* V600 mutations, respectively. Other more rare activating mutations include V600R and V600D. These mutations constitutively activate BRAF protein and signal downstream to activate the RAF/MEK/ERK pathway, which signals for cancer cell proliferation and survival. The patient population recruited in the pivotal clinical trial were tested for the presence of BRAF V600 E or K mutation, which was an inclusion criteria that a patient's tumour had to be confirmed by a validated test prior to treatment initiation. Based on the mechanism of action and the non-clinical data showing the inhibitory activity of binimetinb in tumour cells that harbour BRAF V600E/K/R, the indication has been expanded to include all BRAF V600 mutations as it is expected that binimetinb may target and inhibit MEK, which is downstream of the RAF/MEK ERK pathways and hence would be able to block MEK activation regardless of the type of BRAF V600 substitution.

The patient population included in the pivotal study were patients with histologically confirmed diagnosis of locally advanced, unresectable or metastatic cutaneous melanoma or unknown primary melanoma (AJCC Stage IIIB, IIIC or IV) and excluded patients with uveal and mucosal melanoma. The indication includes all types of melanoma as the prevalence of uveal melanoma and mucosal melanoma

is low and few patients would have been recruited in the trial. In addition, there is no standard of care for these types of melanoma and it is expected that all melanoma patients with a BRAF V600 mutation would benefit from having treatment options that are targeted and have demonstrated efficacy. Patients also had not received prior treatment with a BRAF or MEK inhibitor. A warning has been included in section 4.4 of the SmPC to inform treating physicians that it appears that patients who have received prior BRAF treatment seem to have lower efficacy when treated with the combination. It is also noteworthy that the trial population included naive untreated patients or patients who have progressed on or after prior first-line immunotherapy for unresectable locally advanced or metastatic melanoma. Nevertheless, the indication does not specify the line of treatment as it is left to the treating physician and clinical practice to determine the best treatment algorithm for an individual patient. Section 5.1 of the SmPC describes the patient population that was included in trial.

3.8. Conclusions

The overall B/R of Mektovi is positive.

The CHMP requests the following measures to address the issues related to pharmacology:

- OS results for Combo 300 and updated Combo 300 PFS analysis, including more mature data for the Enco300 Part 2 arm.
- DDI cocktail study: OATP and BCRP will be explored in the ongoing DDI study with rosuvastatin (study ARRAY-818-103)
- Overall survival results stratified by LDH level for Combo 300 and Enco 300 (Part 2).
- To collect PK samples from BRAF melanoma patients with moderate and severe hepatic impairment after repeated dosing of encorafenib in combination with binimetinib to determine the plasma concentrations in relation to administered dose and AEs observed to guide dosing recommendations in these patient populations.

The CHMP recommends the applicant to submit the following measures to address the issues related to pharmacology:

- The applicant should commit to submit the results of the planned biomarker analyses for Study B2301 (from all 3 treatment arms) for evaluation as soon as available, to support the synergistic pharmacodynamic activity of encorafenib in combination with binimetinib. Genomic analysis of baseline samples remaining after centralized BRAF testing. As indicated in the protocol, genomic alterations in BRAF, HRAS, KRAS, NRAS, PTEN, cKIT, PIK3CA, MAP2K1, MAP2K2, ARAF, c-MET, CRAF, EGFR and CCND1 may be explored to find a potential association between baseline mutations and efficacy outcomes.
- The relationship between baseline mutations and efficacy outcomes should be performed, and a date provided to submit the results.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Mektovi is favourable in the following indication:

Binimetinib in combination with encorafenib is indicated for the treatment of adult patients with

unresectable or metastatic melanoma with a BRAF V600 mutation (see sections 4.4 and 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that binimetinib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.