26 July 2018
EMA/CHMP/554696/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Braftovi

International non-proprietary name: encorafenib

Procedure No. EMEA/H/C/004580/0000

Note

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

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List of abbreviations

ADME	Absorption/Distribution/Metabolism/Excretion
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AJCC	American Joint Committee on Cancer
ALT	Alanine Transaminase
AUC	Area Under the Concentration Time Curve
BA	Bioavailability
BCRP	Breast Cancer Resistance Protein
BCS	Biopharmaceutics Classification System
BID	Twice Daily
BIRC	Blinded Independent Review Committee
BRAF	B-Raf Proto-Oncogene, Serine/Threonine Kinase
CDK	Cyclin Dependent Kinase
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CL/F	Total Clearance
Cmax	Maximum Observed Plasma Concentration
cMET	MET Proto-Oncogene, Receptor Tyrosine Kinase
CNS	Central Nervous System
Combo 300	Encorafenib 300 mg QD in combination with binimetinib 45 mg BID
Combo 450	Encorafenib 450 mg QD in combination with binimetinib 45 mg BID
CQA	Critical Quality Attribute
CR	Complete Response
CSR	Clinical Study Report
CT	Computed Tomography
cuSCC	Cutaneous Squamous Cell Carcinoma
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DLT(s)	Dose Limiting Toxicity(ies)
DMC	Data Monitoring Committee
DOR	Duration of Response
DSC	Differential Scanning Calorimetry
EC	European Commission
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
Enco 300	Encorafenib 300 mg
EORTC	European Organization for Research and Treatment of Cancer Quality of Life
EOT	End of Treatment
EQ-5D-5L	EuroQoL-5D-5 Level
ERK	Extracellular Signal-Regulated Kinase
ESMO	European Society for Medical Oncology
FACIT	Functional Assessment of Chronic Illness
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-M	Functional Assessment of Cancer Therapy-Melanoma
FAS	Full Analysis Set
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor
GCP	Good Clinical Practice
HPLC	High performance liquid chromatography
HR	Hazard Ratio

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IR	Infrared
ITT	Intent to Treat
IVRS	Interactive Voice Response System
KM	Kaplan-Meier
LDH	Lactate Dehydrogenase
LME	Linear Mixed-Effects
LVEF	Left Ventricular Ejection Fraction
MAA	Marketing Authorisation Application
MEB	Medicines Evaluation Board
MEK	Mitogen-Activated Protein Kinase
MPA	Medical Products Agency
MRI	Magnetic Resonance Imaging
MS	Mass Spectrometry
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NE	Not Estimable
NMR	Nuclear Magnetic Resonance
NRAS	Neuroblastoma RAS Viral Oncogene Homolog
NS	Not Specified
ORR	Objective Response Rate
OS	Overall Survival
PAR	Proven Acceptable Range
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PDL-1	Programmed Death (Receptor) Ligand 1
PE	Polyethylene
PFS	Progression-Free Survival
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK(s)	Pharmacokinetic(s)
PopPK	Population PK
PPE	Palmar Plantar Erythrodysaesthesia
PPS	Per-Protocol Set
PR	Partial Response
PRO	Patient-Reported Outcome
PS	Performance Status
PVC	Polyvinyl chloride
QbD	Quality by design
QD	Once Daily
QLQ-C30	Questionnaire Core 30
QoL	Quality of Life
QTPP	Quality target product profile
RAF	Serine/Threonine-Protein Kinase
RAS	Rat Sarcoma Viral Oncogene Homologue
RECIST	Response Evaluation Criteria in Solid Tumours
RH	Relative Humidity
RP2D	Recommended Phase 2 Dose
rpm	revolutions per minute
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
Tmax	Time to Maximum Observed Plasma Concentration
TSE	Transmissible Spongiform Encephalopathy
TTR	Time to Response
TYMC	Total Combined Yeasts/Moulds Count

UHPLC	ultra-high performance liquid chromatography
ULN	Upper Limit of Normal
US	United States (of America)
USP-NF	United States Pharmacopoeia-National Formulary
UV	Ultraviolet
vs.	versus
Vz/F	Volume of Distribution
XRPD	X-Ray Powder Diffraction

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 Braftovi, 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: Encorafenib in combination with binimetinib 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).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0054/2016 on the agreement of a paediatric investigation plan (PIP) and an EMA Decision CW/1/2011 on the granting of a class waiver.

At the time of submission of the application, the PIP P/0054/2016 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 encorafenib 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	2 November 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	3 November 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 April 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 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 Braftovi 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.

2.1.1. 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.

2.1.2. 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

[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

5-year survival rate is 17% and, if left untreated, the median survival is 6-9 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.

2.1.3. 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].

[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

These new therapies have been shown to prolong survival in 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

Encorafenib is a potent and highly selective ATP-competitive small molecule RAF kinase inhibitor. The half maximal inhibitory concentration (IC_{50}) of encorafenib against $BRAF^{V600E}$, BRAF and CRAF enzymes was determined to be 0.35, 0.47 and 0.30 nM, respectively. The encorafenib dissociation half-life was >30 hours and resulted in prolonged pERK inhibition. Encorafenib suppresses the RAF/MEK/ERK pathway in tumour cells expressing several mutated forms of BRAF kinase (V600E, D and K). Specifically, encorafenib inhibits *in vitro* and *in vivo* $BRAF^{V600E, D and K}$ mutant melanoma cell growth. Encorafenib does not inhibit RAF/MEK/ERK signalling in cells expressing wild-type BRAF.

Combination with binimetinib

[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

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

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

Pharmacotherapeutic group: antineoplastic agent, protein kinase inhibitor, ATC code: not yet assigned

The applicant applied for the following indication:

- Encorafenib in combination with binimetinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see Section 4.4).

The agreed indication was as follows:

- Encorafenib in combination with binimetinib 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).

Braftovi is supplied as a hard capsule (capsule).

Braftovi 50 mg hard capsules

Each hard capsule contains 50 mg of encorafenib.
Orange opaque cap and flesh opaque body, printed with a stylised “A” on the cap and “LGX 50mg” on the body. The length of the capsule is approximately 22 mm.

Braftovi 75 mg hard capsules

Each hard capsule contains 75 mg of encorafenib.
Flesh coloured opaque cap and white opaque body, printed with a stylised “A” on the cap and “LGX 75mg” on the body. The length of the capsule is approximately 23 mm.

Method of administration

Braftovi is for oral use. The capsules are to be swallowed whole with water. They may be taken with or without food. The concomitant administration of encorafenib with grapefruit juice should be avoided (see sections 4.4 and 4.5)

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

Posology

The recommended dose of encorafenib is 450 mg (six 75 mg capsules) once daily, when used in combination with binimetinib.

Dose modification

The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation (see Tables 1 and 2).

Dose reduction recommendations for encorafenib are presented in Table 1 of the SmPC.

Vomiting

In case of vomiting after administration of encorafenib, the patient should not take an additional 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 encorafenib is missed, the patient should only take the missed dose if it is more than 12 hours until the next scheduled dose.

Type of Application and aspects on development

The development programme for encorafenib in combination with binimetinib in unresectable or metastatic BRAF mutant melanoma comprises data from 10 clinical trials: 4 clinical pharmacology studies in healthy volunteers, 1 study in patients with hepatic impairment, 2 clinical pharmacology/ initial tolerability studies in patients with BRAF positive tumours and 4 clinical efficacy and safety studies.

No formal scientific advice was provided by the EMA. In 2013 and 2014, scientific advice was given by 2 national EU Agencies (MPA, Sweden and MEB, Netherlands) on the design of the pivotal Phase 3 study CMEK162B2301, the choice of PFS as primary endpoint for the study as well as the proposed central response assessment.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 50 mg or 75 mg of encorafenib as active substance.

Other ingredients of the capsule content are: copovidone (E1208), poloxamer 188, cellulose microcrystalline (E460i), succinic acid (E363), crospovidone (E1202), silica colloidal anhydrous (E551) and magnesium stearate (E470b). Ingredients of the capsule shell are: gelatin (E441), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172) and iron oxide black (E172). Ingredients of the printing ink are: shellac (E904), iron oxide black (E172) and propylene glycol (E1520).

The product is available in polyamide/aluminium/PVC/aluminium blister as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of encorafenib is methyl N-{(2*S*)-1-[(4-{3-[5-chloro-2-fluoro-3-(methanesulfonamido)phenyl]-1-(propan-2-yl)-1*H*-pyrazol-4-yl}pyrimidin-2-yl)amino]propan-2-yl}carbamate corresponding to the molecular formula $C_{22}H_{27}ClFN_7O_4S$. It has a relative molecular mass of 540.0 and the following structure:

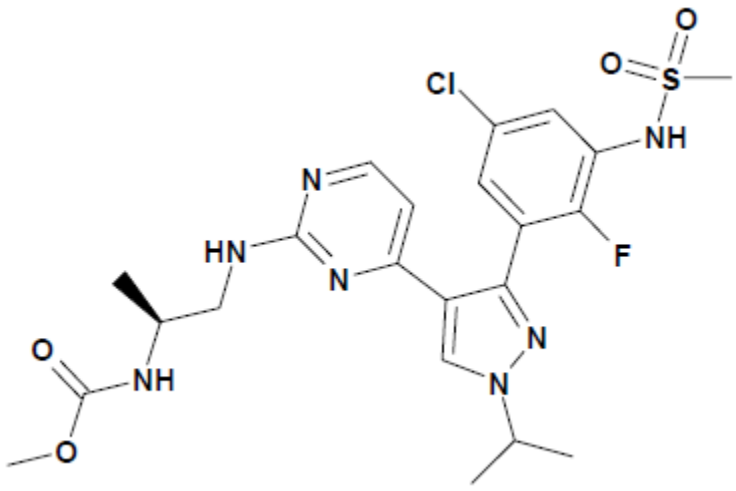


Figure 1: encorafenib active substance structure

The chemical structure of encorafenib was elucidated by a combination of infrared (IR) spectroscopy, proton and carbon nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry (MS), elemental analysis, optical rotation, single crystal X-ray, differential scanning calorimetry (DSC) and dynamic vapour sorption. The crystal structure of encorafenib was determined by X-Ray Powder Diffraction (XRPD)

Experimental polymorphism studies demonstrated that encorafenib is present in a single polymorphic form: "Modification A". Based on the polymorphism study, the absence of routine test for polymorphism in the active substance specification is considered acceptable. It was also shown that the polymorphic form does not change throughout the shelf life as observed in three batches of the active substance placed on stability studies under long-term and accelerated conditions.

The active substance is a white to almost white non-hygroscopic powder. Although the solubility of encorafenib is high at normal gastric pH, it is not sufficiently high across the full range of physiologically relevant pH values of the gastrointestinal tract for encorafenib to be characterized as a highly soluble compound in the BCS classification system. Because encorafenib demonstrates high apparent permeability, its solubility in media with higher pH results in encorafenib being designated as a BCS Class II drug.

Encorafenib exhibits stereoisomerism due to the presence of a single chiral centre. Enantiomeric purity is controlled routinely by chiral HPLC/UV. The stereoisomerism of the active substance originates from the starting material.

Manufacture, characterisation and process controls

The active substance is synthesized using a convergent synthesis process bringing together three synthetic lines in chemical transformation steps.

None of the process steps is considered critical; however a number of critical process parameters are defined.

Encorafenib is proposed for the treatment of an advanced cancer. According to the ICH S9 note for guidance and the ICH M7 guideline, active substances and finished products which are indicated for advanced cancer are exempt from the requirements of ICH M7; impurities may be controlled in line with the ICH Q3 guideline. While genotoxic impurities are not targeted for control to limits specified in the ICH M7 guideline, work conducted during pharmaceutical development did confirm that potential genotoxic impurities are not likely to

be present in the final active substance above the calculated concentration limit based on the threshold of toxicological concern (TTC), which is 22 ppm [(10 µg/day for 1 – 10 years exposure)/(0.45 g encorafenib/day)].

Adequate in-process controls 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.

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

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The manufacturing process has been developed using elements of Quality by Design (QbD) such as risk assessment; however no design space is claimed.

Specification

The active substance specification includes tests for: appearance (visual), identity (IR), related substances (chiral HPLC, UHPLC/UV), residual solvents (GC), water content (KF), particle size (laser diffraction) and assay (UHPLC/UV).

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 and impurities testing has been presented.

Batch analysis data on 11 commercial scale batches of the active substance manufactured using the proposed commercial manufacturing process are provided. Supportive data on 19 additional batches used during development were also provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 batches of the active substance manufactured at scale which is approximately 70% of the commercial scale, by the proposed manufacturer and stored in the intended commercial package for up to 24 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches were representative of those manufactured using the proposed commercial process.

The following parameters were tested: appearance, assay, related substances (including the undesired *R*-enantiomer), water content, and polymorphic form. The analytical methods used were the same as for release and were stability indicating.

Photostability testing following the ICH guideline Q1B was performed on a single batch. The results demonstrate that the active substance is not sensitive to light.

Results on stress conditions: acid hydrolysis, base hydrolysis, oxidation, photodegradation, and degradation from heat and heat and humidity were also provided on a single batch. However, the degradation products resulting from these stress conditions have not been observed in the active substance during pharmaceutical

development and, therefore, no specific manufacturing process controls have been implemented to address these potential degradation pathways.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is an immediate release hard gelatin capsule for oral administration. Capsules are available in two dosage strengths of 50 mg and 75 mg. The 50 mg capsule is size 0 with a Swedish orange opaque cap and flesh opaque body, printed with a stylized “A” on the cap and “LGX 50 mg” on the body. The length of the capsule is approximately 22 mm. The 75 mg capsule is size 00 with a flesh coloured opaque cap and white opaque body, printed with a stylized “A” on the cap and “LGX 75 mg” on the body. The length of the capsule is approximately 23 mm. Two presentations differ in terms of size, colouring and imprints.

The critical quality attributes identified are: appearance, aspect (absence of visual capsule defects), size, identification, assay, uniformity of dosage units, degradation products, dissolution, crystallisation of active substance, water content and microbial limits.

As mentioned earlier in the report the active substance is a BCS Class II substance.

All excipients are well known pharmaceutical ingredients and their quality are compliant with Ph. Eur. standards, except for succininc acid for which there is no Ph. Eur. monograph. This excipient is controlled according to an in-house monograph based on the USP-NF monograph. 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 compatibility of active substance with excipients described was evaluated to determine the potential of excipients to cause significant active substance instability.

The manufacturing site that was used for the production of pivotal clinical batches and primary stability batches is the proposed commercial manufacturing site. Early development batches and some pivotal batches were manufactured at the development site using the initial manufacturing process. The initial manufacturing process was optimised prior to being transferred to the commercial site. The same equipment class was used for each unit operation at each manufacturing site. A comparison of the capsule manufacturing process parameters used at both sites has been provided and considered acceptable. The changes in process parameters have been supported by conducting optimisation studies. Following the manufacturing process development, the critical process parameters were identified and the proven acceptable ranges have been established, however no design space is claimed.

The first in human formulation was based on a microemulsion, which was replaced by a capsule formulation in Phase 1 clinical development. The capsule formulation was used throughout clinical development, including the pivotal clinical study, and is the same as the proposed commercial capsule formulation. The finished product formulation, using a common blend for capsules of different strengths, has remained consistent throughout development.

The 50 mg and 75 mg capsule strengths were developed for easier administration compared to the 100 mg capsules used in clinical trials. The 75 mg presentation represents a balance between capsule size and capsule burden (the number of capsules to be taken daily). The 100 mg strength finished product used in

clinical trials was encapsulated in a size 00EL capsule (length: ~25.5 mm). The size of the 100 mg capsules was considered large and patients may find it difficult in administering the capsules. Although the number of the 75 mg capsules to be taken all at once (six capsules) is considered relatively high, considering the indication of Braftovi is for the treatment of an advanced cancer, and to allow easier administration, the proposed strengths of 50 mg and 75 mg are considered appropriate.

The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is polyamide/aluminium/PVC/aluminium blister. The material complies 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 finished product is manufactured using a non-standard manufacturing process. There are no critical steps or intermediates in the manufacture of finished product.

Major steps of the manufacturing process have been validated by a number of studies on three batches of each of the capsule strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs (Proven Acceptable Ranges).

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance of capsule (visual), appearance of contents (visual), identification (UV, UHPLC/UV), assay (UHPLC/UV), degradation products (UHPLC/UV), crystalline finished product content (XRPD), uniformity of dosage units by content uniformity (Ph. Eur.), dissolution (Ph. Eur. - HPLC/UV), water content (Ph. Eur. – KF), and microbiological enumeration and specified micro-organisms (Ph. Eur).

The undesired *R*-enantiomer is controlled in the active substance specification but not in the finished product release specification. The *R*-enantiomer is analysed on the finished product during stability studies. No changes in its level have been observed. Therefore, it is considered acceptable not to control *R*-enantiomer in the finished product specification.

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

Batch analysis results are provided for six batches of each of the capsule strengths at commercial scale and 38 development batches of the finished product confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from six batches of each of the capsule strengths at commercial scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH), for up to 24 months under intermediate conditions (30 ºC / 75% RH) and for up to six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay and degradation products, dissolution, water content, undesired *R*-enantiomer content (HPLC), crystalline active substance content by XRPD, and microbial content. The same analytical methods were used as for the release of the product, apart from the enantiomer analysis that is only performed during the stability study. The analytical procedures used are stability indicating.

The proposed shelf life of 27 months is considered acceptable based on the ICH Q1E guideline.

In addition, a single batch of each of the capsule strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Good chemical and physical stability was shown upon direct exposure to light. It is concluded that special labelling or packaging is not needed to mitigate exposure to light. A statement 'Store in the original package in order to protect from moisture' has been included in the product information.

Based on available stability data, the proposed shelf-life of 27 months when stored in the original package in order to protect from moisture as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

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.

The applicant has applied QbD principles in the development of the finished product and its manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

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. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical pharmacology and toxicology studies were performed in several in vitro in and in vivo models. Non-GLP pharmacology, functional, molecular (mechanism of action) and anti-cancer efficacy studies were performed to evaluate the level of activity of encorafenib alone and in combination with binimetinib in both in vitro (isolated enzyme and cell culture) and in vivo (mouse xenograft) model systems. No PK, ADME or toxicology studies have been performed with the combination. The safety pharmacology studies and the pivotal toxicology studies were conducted in compliance with GLP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro

Encorafenib and the major circulating metabolite, LHY746 (AR00492720-01) were tested for the potency to inhibit wild type BRAF, V600E mutant BRAF, and CRAF using a radiometric assay format.

The IC50 of the metabolite LHY746 against $BRAF^{V600E}$, BRAF and CRAF enzymes was determined to be 9.27, 15.54 and 9.1 nM, respectively. The IC50 of encorafenib against BRAFV600E, BRAF and CRAF enzymes was 0.8, 1.1 and 0.6 nM.

The selectivity of encorafenib (LGX818) was profiled by evaluating inhibitory activity against 442 kinases at 10 µM (KinomeScan; Ambit). There were 40 hits (<25% percent of control) which were followed up in a dose-response study. The dose-response study confirmed activity on BRAF, $BRAF^{V600E}$ and CRAF. The only other kinases inhibited with an IC50 of similar magnitude (less than 10 nM) was STK36 (~ 5 nM).

Viability and p-ERK Inhibition by Encorafenib in BRAF-Mutant Humans Melanoma Cell Lines (RD-2011-50435, RD-2011-50039, 818-CBiology-0117)

Encorafenib was evaluated in a panel of 512 genetically annotated human cancer cell lines for effects on cell viability and/or proliferation (Cell Titer Glo™ assay).

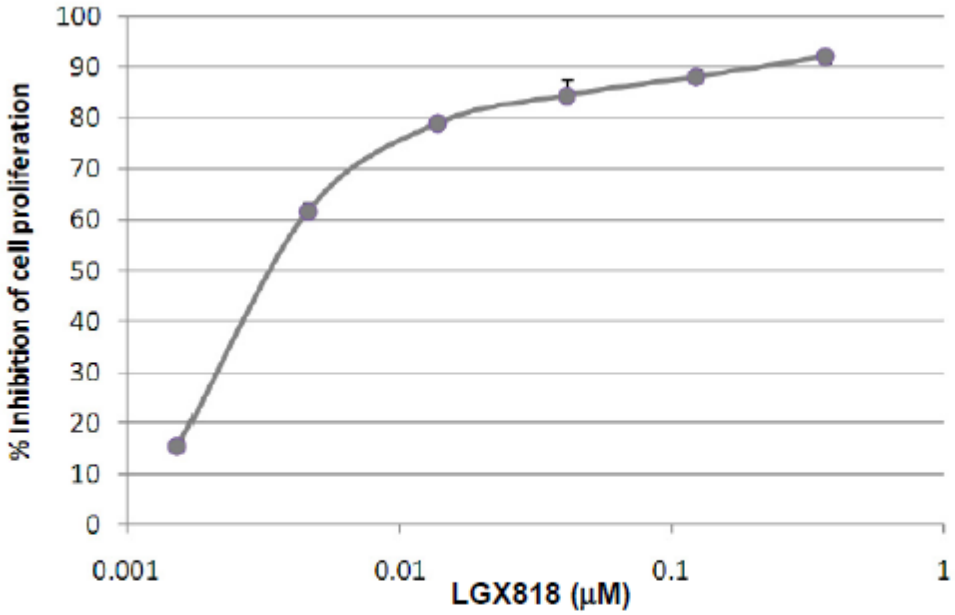
The majority of cell lines that were sensitive to encorafenib contained the $BRAF^{V600E}$ allele. In contrast, cell lines lacking this allele were predominantly insensitive to encorafenib. In a follow-up assay, 6 colorectal derived lines and 26 melanoma-derived cell lines, all of which harbored V600 alterations (E, D or K), were examined for sensitivity to encorafenib. Results showed that 4/6 (67%) of the colorectal, and 19/26 (73%) of the melanoma cell lines were responsive to encorafenib.

Table 2: Grouping of BRAFV600E/D/K or BRAFV600 WT by encorafenib

Compound	BRAF V600 Status	Percentage with CP < 1uM	Fisher's Exact Test p-value
LGX818	V600E/D/K	74% (28/38)	2.7×10^{-32}
LGX818	Wild Type	1.0% (5/455)	

CP=crossing point

Encorafenib was titrated in the A375 BRAF mutant melanoma cell line for viability (Cell Titer Glo™ assay) and for phosphorylation of extracellular signal-regulated kinase (p-ERK; in-cell Western blot) (RD-2011-50039). Both assays detect the modulation of phosphor-ERK or phosphor-MEK. The EC50 was calculated to be 0.004 µM for the in-cell Western blot and 0.003 µM for the proliferation assay.



A375 melanoma cells were seeded at 1,000 cells per well in 96-well plates and treated for 72 h with LGX818. A Cell Titer Glo™ assay was performed, the data was plotted and the absolute IC_{50} values were calculated using the Excel Fit program. Five separate data sets were averaged and the EC_{50} was calculated to be 0.0044 +/- 0.0011 µM.

Figure 2: Cell proliferation assay in A375 melanoma cells treated with encorafenib

The studies showed that encorafenib is approximately 2-fold more potent than the metabolite LHY746 at inhibiting phospho-ERK (33nM vs 76 nM) and approximately 30 fold more potent than LHY746 at inhibiting Malme-3M proliferation (3.7 nM vs 120 nM).

Table 3: Summary of IC50 values

Cell Assay:	LGX818 IC_{50} ± SD (nM)	LHY746 IC_{50} ± SD (nM)	Fold difference in Activity
phospho-ERK	33 ± 2.1	76 ± 4.2	2.3
Proliferation	3.7 ± 0.3	119 ± 9.2	32

In vivo

Nude Mouse, A375 (BRAFV600E Mutant) Melanoma Xenografts

The efficacy and tolerability of LGX818 in the A375 (BRAFV600E) human melanoma mouse tumour xenograft model in nude mice were evaluated. A wide dose-range (0.6 to 300 mg/kg, PO, BID) was tested in this two week study. Mean tumour growth data over time are presented in Figure 3.

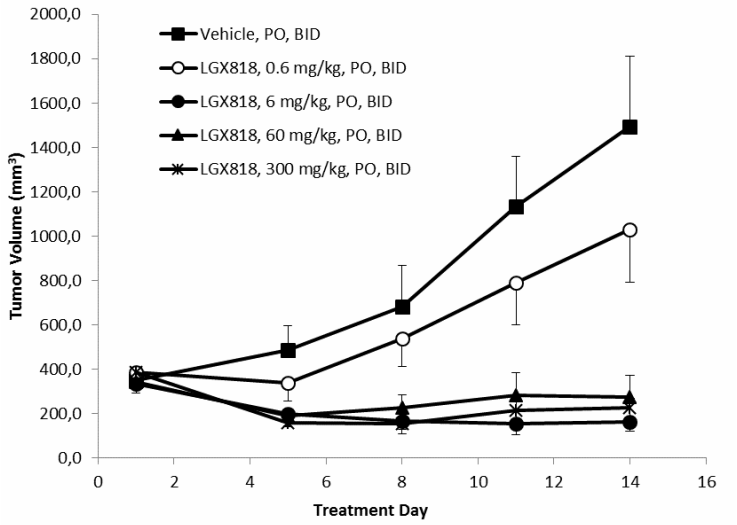


Figure 3: Effects of LGX818 on Tumour Growth in the A375 Human BRAF-Mutant

N = 5 mice per treatment group

Data are mean ± SEM

* $p < 0.05$ for 6 mg/kg and 300 mg/kg LGX818 versus Vehicle by Kruskal-Wallis ANOVA on ranks followed by pairwise comparisons using Tukey test.

This study was designed to determine the dose-dependent effects of encorafenib alone and in combination with a fixed dose of binimetinib on A375 BRAFV600E mutant-melanoma tumour growth in nude mice. There were 8 treatment groups: vehicle (1% CMC/0.5 % Tween 80 in water), binimetinib (MEK162, 3.5 mg/kg, PO, BID), encorafenib (LGX818, 6, 20 or 60 mg/kg, PO, QD) and 3 combination treatment groups with binimetinib (MEK162, 3.5 mg/kg, PO, BID) plus encorafenib (LGX818, 6, 20 or 60 mg/kg, PO, QD).

Mean tumour growth data (± SEM) over time are presented in Figure 4.

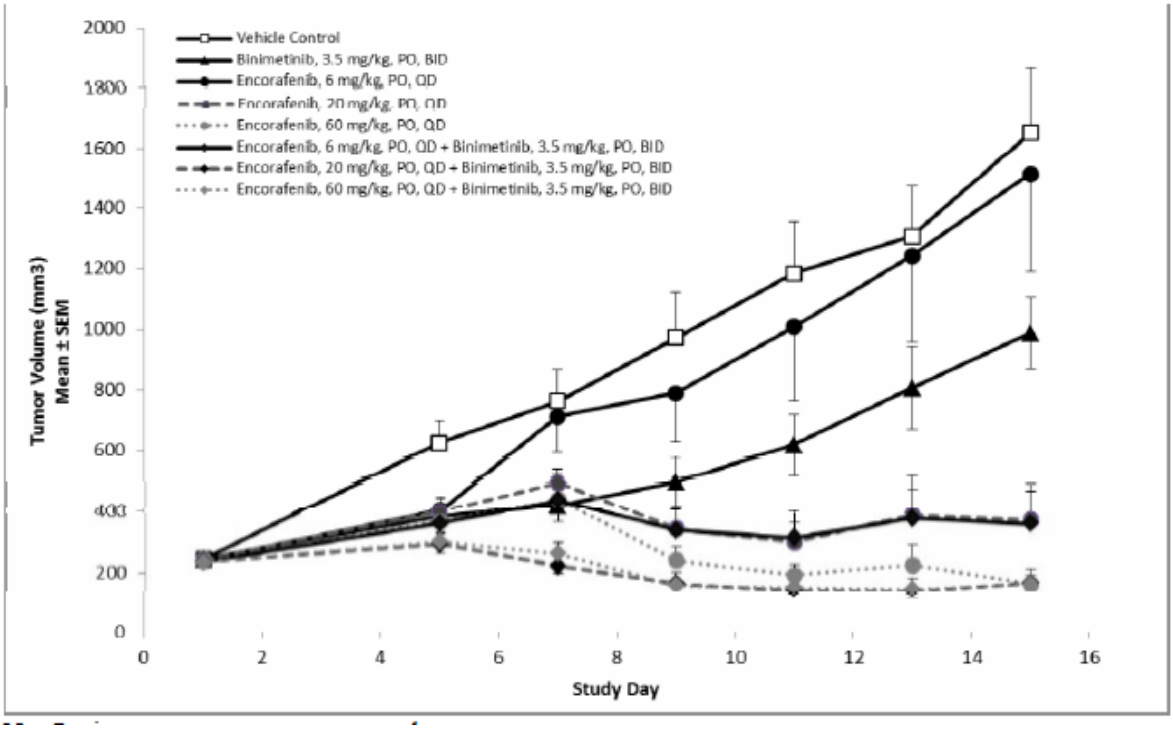


Figure 4: Effects of Encorafenib and Binimetinib as Single Agents, and in Combination, on Tumour Growth in A375 Human BRAF-Mutant Melanoma Xenografts in Nude Mice

N = 7 mice per treatment group at study start

Binimetinib and Encorafenib as Single Agents and in Combination in the HMEX1906 (BRAFV600E) PDX Model

Mean tumour growth data over time are presented in Figure 5.

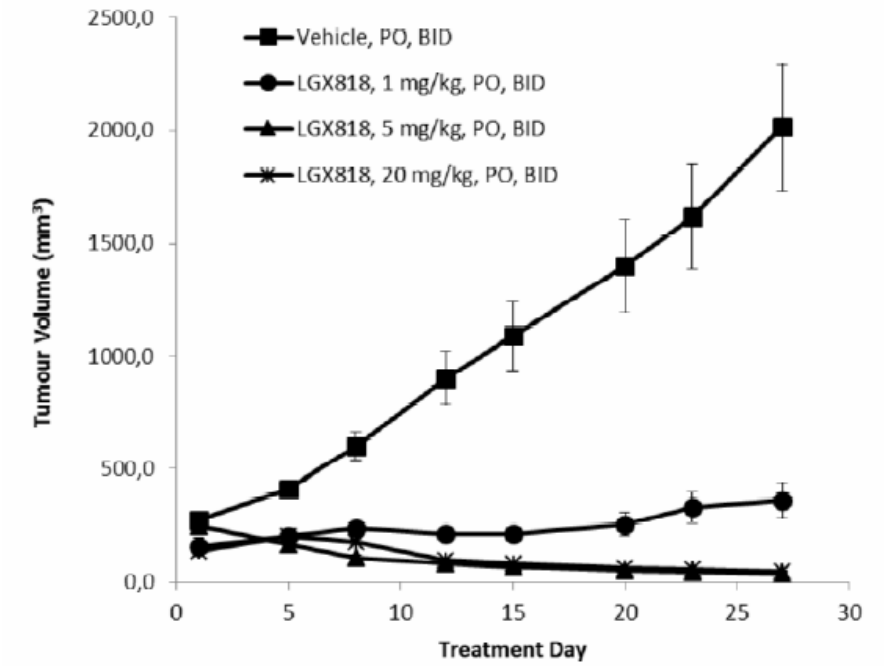


Figure 5: Effects of LGX818 on Tumour Growth in the HMEX1906 BRAF-Mutant

Data are Mean ± SEM

N = 10 mice per treatment group

* $p<0.05$ for 5 mg/kg and 20 mg/kg LGX818 versus Vehicle by Kruskal-Wallis ANOVA on ranks followed by pairwise comparisons using Tukey test.

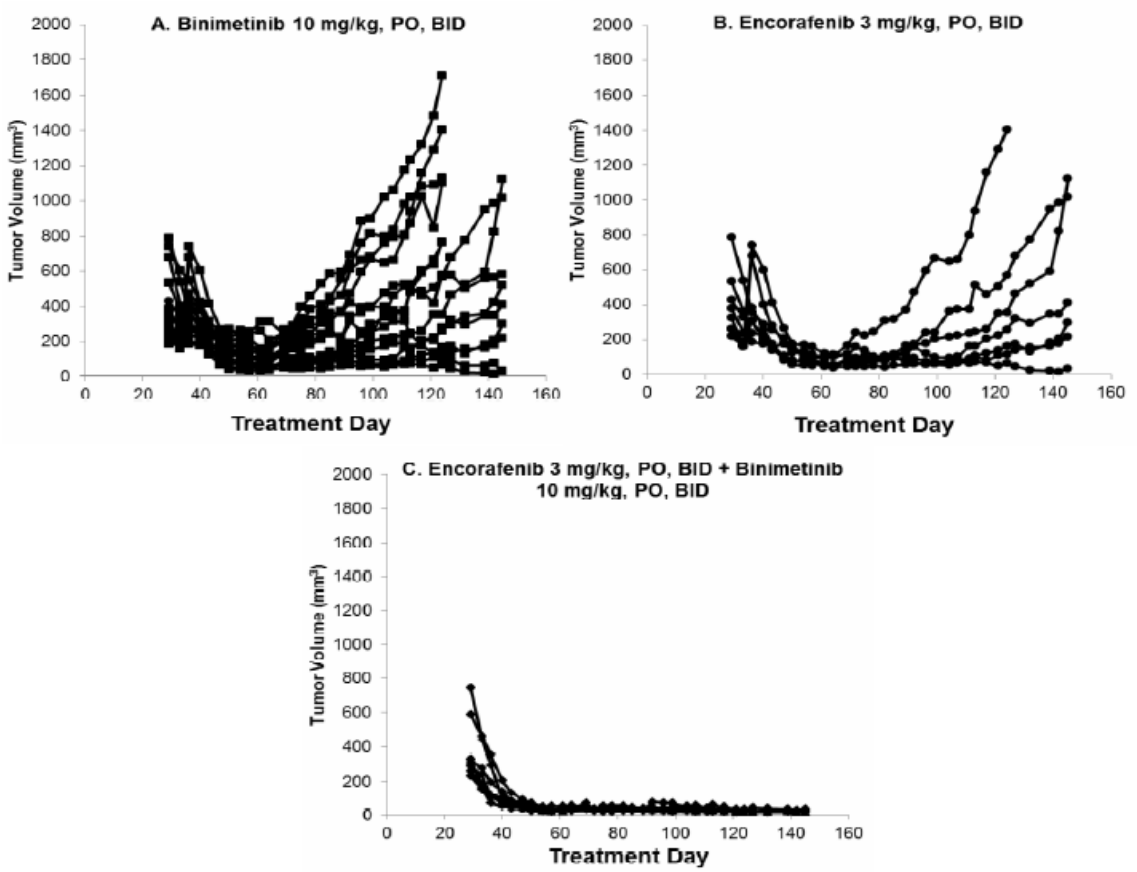


Figure 6: Individual Animal Efficacy of Binimetinib and Encorafenib as Single Agents and in Combination in the HMEX1906 (BRAFV600E) PDX Model

Nude Mouse, MEL13B4 (BRAFV600E) Mutant Human Melanoma Primary Xenograft

This study was designed to determine the dose-dependent effects of encorafenib alone and in combination with a fixed dose of binimetinib on MEL13B4 BRAFV600E mutant-melanoma PDX tumour growth in nude mice. There were 8 treatment groups: vehicle (1% CMC/0.5 % Tween 80 in water), binimetinib (binimetinib, 3.5 mg/kg, PO, BID), encorafenib (encorafenib, 6, 20 or 60 mg/kg, PO, QD) and 3 combination treatment groups with binimetinib (binimetinib, 3.5 mg/kg, PO, BID) plus encorafenib (encorafenib, 6, 20 or 60 mg/kg, PO, QD)(Figure 7).

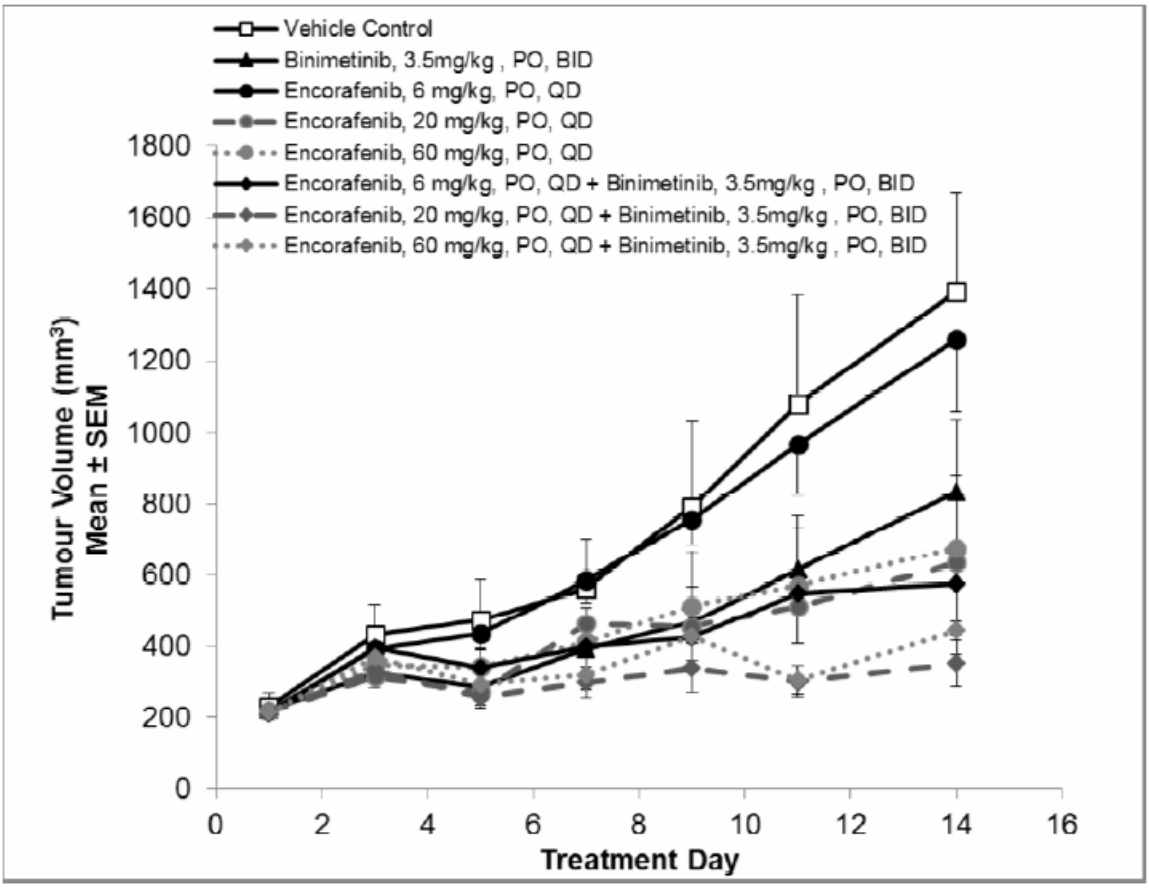


Figure 7: Efficacy of Binimetinib and Encorafenib as Single Agents and in Combination in the MEL13B4 (BRAFV600E) Melanoma PDX Model

N = 8 mice per treatment group at study start except n=6 for the vehicle-treated arm

Secondary pharmacodynamic studies

Off target activity of encorafenib (NVP-LGX818)

Encorafenib (NVP-LGX818) was assessed for its off-target activity on 143 GPCRs, transporters, ion channels, nuclear receptors and enzymes. Activities of > 50% inhibition or activation at 10 µM were consistently found only in the PDE4D enzymatic assay (IC50 = 4.4 µM, n=3).
Encorafenib was tested on 7 targets which have been identified as being potentially involved in suicidality. The compound had no activity up to the highest concentrations tested.

Off-target activity of NVP-LHY746 (A Primary Metabolite of LGX818)

NVP-LHY746 (a primary metabolite of LGX818) was assessed for its off-target activity on 56 GPCRs, transporters, ion channels, nuclear receptors and enzymes. Activities of >50% inhibition at 10 µM were found on KDR kinase (IC50 = 1.8 µM, n=1) and phosphodiesterase PDE4D (IC50 = 4.2 µM, n=2). It was also found to be an agonist of the pregnane X receptor (PXR) (EC50 = 3.8 µM, n=1).

Safety pharmacology programme

Table 4: Overview of the results of the safety pharmacology studies

Organ Systems Evaluated	Species/Strain	Method of Admin.	Doses [a] (mg/kg)	Gender and No. per Group	Noteworthy Findings
hERG Channel	HEK293 cells	In vitro	Up to 100 µM	NA	• hERG channel inhibition IC_{50} = 73.4 µM
Neurobehavioral and Respiratory Function	Rat, Sprague-Dawley	PO	0 or 100	10M for behavioral; 5M for respiratory	• No significant effects at 100 mg/kg • NOAEL = 100 mg/kg
Cardiovascular Function	Monkey, Cynomolgus	PO	50, 100, 200	6 M	• No significant effects on systemic blood pressures (systolic, diastolic, mean arterial and pulse pressure), electrocardiographic intervals (PR, QT, QTc, QRS), body temperature or ECG waveforms • Higher heart rates at all dose levels with no diurnal shift

a Single dose unless specified otherwise
b All studies were conducted using LGX818 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

The applicant did not submit pharmacodynamic drug interaction studies (see non-clinical discussion).

2.3.3. Pharmacokinetics

PK data were obtained from studies conducted in mice, rats, dogs and monkeys with encorafenib administered either orally or/and intravenously.

Single Dose:

Table 5: Tabulated PK data for single dose encorafenib

Study ID	**Type of Study**	**Species** **N/Gender**	**Route, Dose**	**Results**
RD-2011-50077	**Single dose** PK of free base	**Mice** **Balb/c** 3 M	**Oral** 10 mg/kg BW **IV** 2 mg/kg BW	Low clearance (4.3 mL/min/kg) and very low volume of distribution (0.1 L/kg), with a short mean residence time (MRT) of 0.4 h and elimination half-life of 0.9 h. Following oral administration high oral exposure with a mean Cmax and AUC(0-∞)

Study ID	Type of Study	Species N/Gender	Route, Dose	Results
				of 26.4 μM and 30.4 h*μM, respectively. Oral bioavailability was 43%.
RD-2011-50078	**Single dose** PK of free base	**Rats** **Wistar** 3 M	**Oral** 10 mg/kg BW **IV** 3 mg/kg BW	Low clearance (1.06 mL/min/kg) and very low volume of distribution (0.13 L/kg), with a short mean residence time (MRT) of 2.1 h and elimination half-life of 2.3 h. Following oral administration high oral exposure with a mean Cmax and AUC(0-∞) of 48.4 μM and 144 h*μM, respectively. Oral bioavailability was 49%.
DMPK R 1000227	**Single dose** PK of [^{14}C] free base	**Rats** **Han Wistar** **Intact and bile duct-cannulate** 3 M	**Oral** Suspension 50 mg/kg BW **IV** Solution 5 mg/kg BW	Free base of encorafenib was the main radioactive compound in plasma extracts, accounted for 85% of the total plasma AUC0-24h after either iv. or oral dosing. Elimination primarily through extensive oxidative metabolism and, to a much smaller extent, through parent drug excretion (~10% of the recovered dose in the 0-72h excreta) following iv. Metabolic evaluation see section 3.4.
RD-2011-50053	**Single dose** PK of free base	**Dogs** **Beagle** 3 M	**Oral** 0,3 mg/kg BW **IV** 0,1 mg/kg BW	Moderate total clearance (21 mL/min/kg), a moderate volume of distribution (2.6 L/kg) and a terminal half-life of 5.2 hr. Following an oral administration of free base in solution, the mean maximal plasma concentration (Cmax) of 0.12 _M was achieved on average at 0.3 hour post dose. The oral bioavailability was good at 42%.
DMPK P 1000065	**Single dose** PK of free base	**Monkey** **Cynomolgus** 5 M fasted	**Oral** 10 mg/kg BW **IV** 0,5 mg/kg BW	The absolute mean bioavailability after oral solution was 8.7 ± 0.1 % (Formulation: 2 mg/mL solution of LGX818-NX in 20% PEG300 + 3% VitE-TPGS).
DMPK R 1300268	**Single dose** PK of [^{14}C]	**Monkey** **Cynomolg**	**Oral** 20 mg/kg	Systemic plasma clearance was moderate (20 mL/min/kg), The volume of distribution at steady state was moderate at

Study ID	Type of Study	Species N/Gender	Route, Dose	Results
	free base	**us** 5 M	BW **IV** 3 mg/kg BW	approximately 1.00 L/kg and the mean terminal t1/2 was 1.1 hours. After IV administration, the terminal t1/2 was similar at 0.64 hours. Following an oral dose, the Tmax was 2 hours. The overall oral absorption of [14C]encorafenib, estimated from dose-normalized AUCs for radioactivity after IV and oral doses, was estimated to be approximately 60-80% based on blood and plasma, respectively. The bioavailability in this study was calculated to be approximately 22%. Metabolic evaluation see section 3.4.

Tissue distribution/Melanin Binding

Tissue distribution studies were performed for drug-derived carbon-14 material using quantitative whole body autoradiography (DMPK R1100588) in Long Evans Hooded (pigmented) rats at 0.25, 1, 2, 4, 7, 24, 72 and 168 hours following a single oral (50 mg/kg) dose of [14C]encorafenib, and at 0.05 and 2 h following a single intravenous (5 mg/kg) dose. Additionally, one HanWistar (albino) rat was sacrificed at 168 hours post 50 mg/kg oral dose for comparison. [14C]encorafenib-derived radioactivity was absorbed and widely distributed to tissues in rats following a single oral (PO) dose with most tissue radioactivity concentrations reaching Cmax between 0.25 to 2 h post-dose. The tissue:blood ratio based on AUCinf of radioactivity was >1 for the bile, colon wall, liver, and kidney pelvis, cortex, and medulla. The elimination of drug-related radioactivity was moderate in most tissues (t1/2 < ~10 h), except for the liver (t1/2 = 47.2 h). At 72 h post dose, radioactivity in most tissues was not measurable, except for the kidney medulla and liver. Overall, the tissue distribution pattern after an IV dose was similar to that after an oral dose. Drug-related [14C]encorafenib radioactivity showed little or no distribution to the central nervous system (brain and spinal cord) and no retention in the melanin-rich tissues (skin and uveal tract). No radioactivity was detected in either pigmented or non-pigmented rats at 168 hour.

Plasma protein Binding and Blood Plasma Ratio

Plasma protein binding, which appeared to be independent of encorafenib concentration, ranged from 74.6 to 98.6% across species, with high binding in rodents and moderate binding in other species (DMPK R1100210). In humans, the mean plasma protein binding of encorafenib was moderate, approximately 86.1%, when evaluated by the ultracentrifugation method over the concentration range evaluated (50 to 50,000 ng/mL). The blood-to-plasma concentration ratios, which also appeared to be independent of encorafenib concentration, ranged from 0.61 to 0.81 across species (0.75 in humans). In humans, the blood-to-plasma ratio was approximately 0.75 over the concentration range evaluated (50 to 50000 ng/mL).

In vivo Metabolism in Sprague-Dawley Rat

Encorafenib was the major circulating drug-related component in the plasma after either IV or oral dosing, contributing 85% to the total radioactivity by AUC0-24h regardless of administration route. All circulating metabolites were <5% of total radioactivity in plasma of rats for IV and PO administration. The major metabolic pathways of encorafenib in the rat involved oxidative N-dealkylation which included loss of the isopropyl moiety (M32.7), loss of the isopropyl-carbamic acid methyl ester side chain (M42.5A), and loss of both the isopropyl moiety and the isopropylcarbamic acid methyl ester side chain (M23.8). Together, these three metabolites accounted for ~62% of the dose eliminated in rat excreta after intravenous dosing.

The majority of the dose recovered in rat excreta was found in the faeces with a smaller amount in the urine following both routes of administration. In urine, metabolite M23.8 (a double N-dealkylated metabolite derived from the loss of both the isopropyl moiety and the isopropyl carbamic acid methyl ester side chain) was the predominant component, with minimal unchanged encorafenib. In faeces, ~9.96% (intravenous) and ~45.7% (oral) of the dose was associated with unchanged encorafenib, while metabolite M32.7 (N-desisopropyl encorafenib) was the most abundant metabolite.

The most abundant component in faeces of bile duct-cannulated rats was unchanged encorafenib, accounting for 5.50% and 57.8% of the administered dose for the intravenous and oral groups, respectively.

Drug Metabolizing Enzymes

The effect of selective chemical inhibitors of CYP enzymes on the rate of total oxidative [14C]encorafenib metabolism in human liver microsomes was also determined. The maximal percent inhibition achieved by CYP3A inhibitors (ketoconazole and azamulin) was 76.3%. The inhibitor quinidine (CYP2D6) inhibited total [14C]encorafenib oxidative metabolism by 36.5%. After accounting for enzyme abundance in the liver, CYP3A4 was predicted to be the major enzyme contributing to total oxidative clearance of encorafenib in human liver microsomes (~83.3%), followed by CYP2C19 and CYP2D6 (~16.0% and 0.71%, respectively). Strong CYP3A4 inhibitor posaconazole when co-administered with encorafenib resulted in ~2.7-fold increase in encorafenib AUC0-24h; co-administration of moderate CYP3A4 inhibitor diltiazem resulted in ~1.8-fold increase in encorafenib AUC0-24h.

In vivo Metabolism in Monkey

In monkey plasma, [14C]encorafenib accounted for 40% and 10% of the total radioactivity AUClast, after IV and PO administration, respectively. The most prominent plasma metabolites were M22.5A (formed through carbamate hydrolysis followed by oxidative deamination, N-dealkylation, and hydroxylation, accounting for 23% of total radioactivity after IV dosing and 42% after PO dosing) and M23.8 (N-dealkylated metabolite derived from loss of both the isopropyl moiety and the isopropyl-carbamic acid methyl ester side chain, accounting for 7.8% of total radioactivity after IV dosing and 12% after PO dosing). Overall [14C]encorafenib was extensively metabolized to multiple metabolites, where only 2.51% or 6.19% of intact encorafenib remained in excreta after either an intravenous or an oral dose, respectively.

Enzyme Induction and Inhibition

CYP Inhibition

Encorafenib was assessed as a potential inhibitor of cytochrome P450s *in vitro* in human liver microsomes with appropriate probe substrates. Encorafenib showed inhibitory potency for CYP2B6, CYP2C9 and CYP3A4/5 with IC50 values of ~1, ~5 and ~8-15 µM, respectively. Encorafenib showed inhibitory potency for CYP1A2,

CYP2C8, CYP2C19 and CYP2D6 with IC50 values of ~22, ~20-30, ~50 and ~25 µM, respectively. Very little or no inhibition of CYP2A6 and CYP2E1 was observed at encorafenib concentrations of up to 100 µM.

Encorafenib was also assessed as a potential time-dependent inhibitor of cytochrome P450s in human liver microsomes. Encorafenib showed no apparent time-dependent inhibition of CYP1A2, CYP2C9 or CYP2D6 at encorafenib concentrations of up to 50 µM and weak time-dependent inhibition of CYP3A4/5.

UGT Inhibition

Encorafenib was assessed as a potential inhibitor of UGT1A1 *in vitro* using pooled human liver microsomes and recombinant UGT1A1. *In vitro* experiments indicate that encorafenib is a relatively potent inhibitor of UGT1A1. In pooled microsomes, with estradiol as the probe substrate the IC50 was ~7 µM and with binimetinib (MEK162) as the probe substrate the IC50 was ~1-4 µM. In an assay using recombinant UGT1A1, with estradiol as the probe substrate the IC50 was ~4 µM and with binimetinib as the probe substrate the IC50 was ~3.5 µM.

CYP Induction

The potential for encorafenib to activate the human pregnane X-receptor (PXR) was assessed in a cell-based reporter gene assay. Assay results indicated a moderate risk of CYP3A4 induction *in vitro* by encorafenib (≥ 10-50 µM), as the PXR activation ranged between 25-40% of the positive control RIF response at these concentrations.

Encorafenib was investigated as an *in vitro* inducer of cytochrome P450 enzymes in cryopreserved human hepatocytes in 2 studies based on mRNA as well as activity. Encorafenib was found to be an *in vitro* inducer of CYP1A2, CYP2B6, CYP2C9 and CYP3A4 based on mRNA and activities (levels > 2-fold) in at least one of the three donor hepatocytes. Maximal CYP1A2 induction by encorafenib (1-100 µM) was 13.0- to 39.2-fold based on mRNA and 2.12- to 3.76-fold based on activity. Maximal CYP2B6 induction donors. Maximal CYP2C9 induction was 2.8- to 5.41-fold based on mRNA but only exceeded 2- fold based on activity in 2 of 3 donors. Maximal CYP3A4 induction was 24.9- to 167-fold based on mRNA and 2.21- to 4.97-fold based on activity. It can be concluded that encorafenib is an inducer of CYP1A2, CYP2B6, CYP2C9 and CYP3A4 mRNA and activity when evaluated *in vitro*.

Routes and Extent of Excretion

A mass balance excretion study were performed in intact and bile duct-cannulated rats dosed with [14C]encorafenib. Following IV dosing of [14C]encorafenib at 5 mg/kg in intact rats, urinary and faecal excretion accounted for approximately 24.3% and 74.1% of total radioactivity, respectively. Within 48 hours after a single dose (IV or oral) approximately 86.9-95.9% of the dose was excreted into urine and faeces. By 7 days following [14C]encorafenib administration, by either the IV or oral routes, total recovery of radioactivity in the excreta was approximately 99% or 97.4%, respectively.

A mass balance excretion study was also performed in cynomolgus monkeys dosed with [14C]encorafenib. Following IV dosing of [14C]encorafenib at 3 mg/kg, more radioactivity was excreted in the faeces (68.2%) than urine (14.4%) over a 7 day period (0-168 h). Approximately 0.08% of the encorafenib dose was excreted unchanged in urine and 2.43% in faeces after an IV dose in the monkey. Following PO dosing of [14C]encorafenib at 20 mg/kg, again more radioactivity was excreted in the faeces (59.7%) than urine (17.4%) over a 7 day period. The total recovery of [14C]encorafenib-derived radioactivity in excreta (including cage washes) after an IV and PO dose was approximately 95.0% and 90.6% over a 7 day period, respectively. Approximately 0.16% of encorafenib was excreted unchanged in urine and 6.03% in faeces after a PO dose in the monkey.

2.3.4. Toxicology

Single dose toxicity

No single dose toxicology studies were submitted (see non-clinical discussion).

Repeat dose toxicity

Repeat-dose toxicity studies in rats

A 28 day and 13-week repeat-dose toxicity study were performed in rats.

Table 6: 28 day oral gavage repeat-dose toxicity and toxicokinetic study with encorafenib in rats

Study Type (Study ID) GLP	Species; Number/Dose Group	Dose (mg/kg/day) p.o.	Major findings
28 day repeat dose toxicity + 4 week recovery (Pcs-r 1070180) GLP	Wistar-Han rat; 10/sex/dose + toxicokinetics recovery: 6/sex/control and HD	0 (vehicle) 20 100 400* *♀ HD and HD recovery only dosed D1-9 vehicle: 0.5 % CMC/0.5 % Tween 80 in water	**mortality:** 2♀HD by D10 **sacrificed moribund:** 1♂HD, 8♀HD by D10, 1♀HD recovery on D2 of recovery period **body weight:** ↓♀LD-HD, ♂ MD, HD **food consumption:** ↓↓♀HD, ↓♂HD **clinical signs:** behavior, appearance, motor abilities, ptosis (♀HD irrev.) **skin/fur:** flaky and reddened skin, footpad swelling, sore tail (♂♀LD-HD, irrev. ♂♀) **hematology:** ↓hemoglobin (♂HD) ↓mean red cell volume (♂HD, ♀MD) ↑reticulocytes (♀MD, ♂HD irrev.) ↓red blood cell count (♀HD irrev.) ↓mean RBC corpus – hemoglobin (♂HD, ♀MD), ↑neutrophils (♂MD-HD) ↑lymphocytes (♂MD) ↑eosinophils (♂MD-HD, ↑♀MD) **serum chemistry:** ↓AST (♂HD), ↓globulin (♂HD), ↑A/G ratio (♂HD),↓serum triglyceride (♂HD, ♀MD) ↓creatinine (♂HD), ↓phosphorus (♂HD, ♀MD) **sacrificed ♀HD**: ↓platelets, ↓reticulocytes, ↑prothrombin time, ↓fibrinogen, ↓protein,↓ albumin, ↓globulins, ↓serum triglyceride 1♀HD severe vacuolar hepatopathy, renal tubular epithelial vacuolation **organ weights:**

			↓mean epididymides weights (♂LD-HD), ↓mean prostate weights (♂HD) **macroscopic findings:** plantar skin: scaly/thickened area irrev. (♂MD,HD, ♀LD,MD) **microscopic findings:** testes: tubular degeneration and vacuolation epididymides: irrev. oligospermia, cellular debris (♂LD-HD irrev.), stomach: hyperkeratosis, squamous epithelial hyperplasia (♂♀MD,HD), skin/feet: hyperkeratosis, squamous cell hyperplasia, inflammatory cell infiltration (♂MD,HD, ♀LD,MD)
NOAEL=Ø			

A/G: albumin/globulins, AST: aspartate amino transferase, D: day, HD: high dose, irrev.: irreversible, LD: low dose, MD: mid dose, RBC: red blood cell count

Table 7: 13-week oral gavage repeat-dose toxicity and toxicokinetic study with encorafenib in rats

Study Type (Study ID) GLP	Species; Number/Dose Group	Dose (mg/kg/day) p.o.	Major findings
13 week repeat dose toxicity + 4 week recovery (Pcs-r 1270356) GLP	Wistar-Han rat; 10/sex/dose + toxicokinetics recovery: 6/sex/control and HD	0 (vehicle) 6 20 60 vehicle: 0.5 % CMC/0.5 % Tween 80 in water	**preterminally euthanised:** 1♂HD (recovery) on D82 (gavage error) **body weight + body weight gain:** ↓♂♀LD-HD **food consumption:** ↓♂MD,HD **skin:** scabbed, dry, flaky, red and/or white, and/or on hind/fore paws, tail (♂♀LD-HD, irrev.) **hematology:** ↑neutrophils (♂♀HD), ↑eosinophils (♂MD,HD,♀MD,HD irrev. ↑WBC count (♀MD, ♀♂HD irrev. in ♀HD.), ↑reticulocytes (♀MD,HD) **serum chemistry:** ↑urea (♂MD,HD), ↑glucose (♀MD,HD,♂HD), ↑cholesterol (♂LD-HD), ↓serum triglyceride(♂HD), ↑serum triglyceride (♀MD,HD) **organ weights:** ↓mean abs./rel. epididymides weights (♂MD-HD), ↓mean abs./rel. prostate weights (♂MD-HD) **macroscopic findings:** skin: hind paws: yellow and thick footpad (♂HD), testis: abnormal consistency, small

			(♂MD,HD), <u>epididymides:</u> abnormal consistency, small (♂MD,HD), **microscopic findings:** <u>testes:</u> tubular degeneration <u>epididymides:</u> oligo/aspermia, cellular debris (♂LD-HD; irrev.), <u>stomach:</u> epithelial hyperplasia, non-glandular, hyperkeratosis (↑MD,HD, ♀HD, irrev.), <u>skin (hind paws):</u> hyperkeratosis, epithelial hyperplasia (♂♀LD-HD irrev.)
NOAEL= 20 mg/kg/day (♂rats Cmax=42.1 µg/mL; AUC=178 µg.h/mL; ♀rats Cmax=54.5 µg/mL, AUC= 414 µg.h/mL)			

abs.: absolute, D: day, HD: high dose, irrev.: irreversible, LD: low dose, MD: mid dose, rel.: relative, WBC: white blood cell

Table 8: 28-day repeat-dose toxicity and toxicokinetic study in Cynomolgous monkeys with oral (gavage) administration of encorafenib

Study Type (Study ID) GLP	Species; Number/Dose Group	Dose (mg/kg/day) p.o.	Major findings
28-day repeat dose toxicity + 4 week recovery (Pcs-1070179) GLP	Cynomolgous monkey; 3/sex/dose + toxicokinetics recovery: 2/sex/control and HD	0 (vehicle) 5 20 100 vehicle: 56:29:15% w:w:w PEG400: Cremophor EL: Oleic acid	↓**body weight** (♂♀HD) ↓**food consumption:** (↓♂♀HD) **clinical signs:** fecal findings, diarrhea (♂♀HD); emesis with feed +/-compound (♀HD)
NOAEL= 100 mg/kg (mean AUC_{0-24h} (ng.h/mL) for ♂/♀: 63900/61100; 28500/12000 on Days 1 and 29			

HD: high dose

Table 9: 13-week repeat-dose toxicity study in Cynomolgous monkey with oral (gavage) administration of encorafenib

Study Type (Study ID) GLP	Species; Number/Dose Group	Dose (mg/kg/day) p.o.	Major findings
13-week repeat dose toxicity + 4 week recovery (Pcs-	Cynomolgus monkey; 4/sex/dose + toxicokinetics	0 (vehicle) 6* 20* 60* vehicle: ultra pure water	slightly ↓**body weight gain** (♂♀HD)

1270357) GLP	recovery: 2/sex/control and HD	*encorafenib as blend containing15 % active ingredient	
NOAEL=60 mg/kg/day (mean AUC_{0-24h} (ng.h/mL) for ♂/♀: 2490/1260, 5330/3550, 1190/794 on Days 1, 28, 84			

HD: high dose

Table 10: 13-week repeat-dose study in Cynomolgous monkeys with oral (gavage) administration of encorafenib

Study Type (Study ID) GLP	Species; Number/Dose Group	Dose (mg/kg/day) p.o.	Major findings
13 week repeat dose toxicity + 10 week recovery (Pcs-1370471) GLP	Cynomolgous monkey; 4/sex/dose + toxicokinetics recovery: +2/sex/control + HD	0 (vehicle) 20* 60* vehicle: purified water *encorafenib as 15% solid dispersion	**↓body weight** (♀LD, HD) **clinical signs:** emesis + emesis with apparent compound (♀LD,♂♀HD), salivation (♀HD) **ophthalmic findings:** blister-like lesions and yellow substance in fovea; histopathology: separation/detachment in the retina between the outer rods and cones layer and the retinal pigmented epithelium at the central macula fovea (♂HD1/6, ♀HD1/6)
NOAEL= 20 mg/kg/day (mean AUC_{0-24h} (ng.h/mL) for ♂/♀: 5830/11100, 2730/4940, 3120/4280 on Days 1, 23, 86			

HD: high dose; LD: low dose

Genotoxicity

Table 11: Overview of genotoxicity studies performed with encorafenib

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria / Pcs-r1070208 / Yes	Salmonella strains TA1535, TA97a, TA98, TA100, TA102	0 - 5000 µg/ +/- S9	Negative for relevant increase in reverse mutations
Chromosome aberrations in mammalian cells / Pcs-r1070206 / Yes	Human peripheral blood lymphocytes	Experiment 1: -S9: 25 to 600 µg/mL; +S9: 25 to 700 µg/mL (3+17h) Experiment 2: -S9: 5 to 150 µg/mL; +S9: 25 to 600 µg/mL (20+0h and 3+17h respectively)	No relevant metaphases with chromosome aberrations Mitotic inhibition >50% at ≥ 400 µg/mL with 3+17 h exposure; and at ≥ 50 µg/mL with 20 h exposure (-S9)
Chromosomal aberrations in vivo	Male Hanover Wistar rats, 6/dose,	0, 200, 1000, 2000 mg/kg, oral gavage	No increase in micronucleated PCEs.

/ Pcs-r1270199/ Yes	micronuclei in bone marrow (polychromatic erythrocytes, PCEs)	separated by 24h, harvest point 24h post treatment	No significant decrease in PCE/NCE ratio, exposure not determined, no clinical signs.

Carcinogenicity

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

Reproduction Toxicity

The applicant did not submit studies in reproduction toxicity (see non-clinical discussion).

Table 12: Embryofetal development (EFD) studies in pregnant rats and rabbits, respectively

Study type/ Study ID	Species; Number Female/ group	Route & daily dose (mg/kg)	Dosing period	Major findings	NOAEL (mg/kg) AUC_{0-24}
EFD Study No.: 9000201 Novartis Ref. No.: 1370077	Rats, Wistar Hannover Crl:WI (Han) 24 + additional TK	Oral / gavage 0 0.5 5 20	gd 6 - 17	**F_0:** **Mortality**: 1 HD TK found dead on gd 16 after blood sampling; prior to death ↓activity, sustained convulsions, pallor skin + laboured breathing, no macroscopic findings **Body weight gain:** HD ↓↓ gd 6 – gd 9 (only transitory) **F_1:** **Fetal weights**: HD males ↓↓ **External malformations** (not considered treatment related): *Abnormal flexure of hindlimb* unilateral: 1 Co, 1 MD, 2 HD out of 1 litter *Omphalocele*: 2 MD out of 1 litter *Multiple anomalies* (anasarca, small upper + lower jaw + small eye bulge + abnormal flexure of left hindlimb): 1 HD **Visceral anomalies:** Small left *lens*: 1 LD; dark discoloration of right *vitreous body*: 1 LD; bilateral small *lens* + dark discoloration of left *vitreous body*: 1 HD **Skeletal variations** (likely due to ↓↓ fetal weights in HD): Parietal and interparietal bone incomplete ossification: HD ↑↑ Thoracic centrum unossified / incomplete / semi-bipartite / bipartite: HD ↑↑	F_0: 20 mg/kg/d AUC_{0-24}: 370 µg*h/ml Safety margin*: 20 X F_1: 5 mg/kg/d AUC_{0-24}: 90.2 µg*h/ml Safety margin*: 7 X
DRF EFD Study No.:	Rabbits (Hra[NZW] SPF)	0 50	gd 7 - 20	**F_0:** **Mortality**: 200: 2/3 found dead and 1/3 euthanized on	

9000202 Novartis Ref. No.: 1370123	3 - 6	75 100 200		gd 13. Prior to death all does no food consumption + ↓/liquid fecal output 100: 1/3 euthanized on gd 17 due to extreme bw loss, thinness, ↓fecal size **Clinical signs:** ↓ fecal output **Food consumption**: ≥ 50 ↓ **Body weight**: 100 ↓ **F_1**: **Malformations**: 50: 1 fetus with exencephaly	
EFD Study No.: 9000203 Novartis Ref. No.: 1370141	Rabbits (Hra[NZW] SPF) 20 + additional TK	Oral / gavage 0 5 25 75	gd 7 – 20	**F_0:** **Mortality**: 4 HD; signs prior to death: ↓food consumption, ↓feces/liquid feces; partly closed eyes (1 HD), prominent backbones (2 HD), thinness (1 HD) **Body weight gain**: HD ↓↓ **Food consumption**: HD ↓↓ (gd 15 – 23) **F_1:** **Fetal weights:** HD ↓ (but within historical control range, likely due to ↓↓ maternal food intake) **Total malformations** (no. of foetuses / no. of litters): Control: 2/1 (1 with *microcaudia*; 1 with *cleft skin at ventral sacral region*) – LD:0/0 – MD: 2/2 (1 with *microphtalmia*; 1 with *gastroschisis*) – HD: 4/4 (1 with *diaphragm hernia + small lung lobe*; 1 with *absent spleen*; 2/2 with *multiple heart malformations*) **Visceral anomalies**: *Heart malformations* in HD group: *misshapen heart, dilation of ascending aorta, stenosis of pulmonary trunk, absent interventricular septum, dilatated aortic arch* **Skeletal variations**: ↑↑ in no. of fetuses and litters with semi bipartite thoracic centra in MD + HD	F_0 + F_1: 25 mg/kg/d AUC_{0-24}: 1010 µg*h/ml Safety margin*: 79 X

HD = high dose: MD = mid dose; LD = low dose; gd = gestation day; bw = body weight; ↑↑ = significant increase(d); ↓↓ = significant decrease(d); * = based on comparison to exposure in patients at 450 mg (AUC_{0-24} = 12.9 µg.hr/ml)

Toxicokinetic data

Table 13: Animal to human exposure multiples at the NOAEL of the different pivotal toxicity studies performed for encorafenib in rats, monkeys and rabbits

Study	NOAEL (mg/kg/day)	AUC_{0-24h} (µg.h/mL)	Animal to human exposure multiples
4-week study in rats (Pcs-r1070180)	N.D.		
13-week study in rats on Day 90	♂♀ 20	♂: 178	**14**

(Pcs-r1270356)		♀: 414	**32**
4-week study in monkeys on Day 29 (Pcs-1070179)	♂♀ 100	♂: 28.5	**2.2**
		♀: 12	**0.9**
13-week study in monkeys on Day 86 (Pcs-1370471)	♂♀ 20	♂: 3.12	**0.24**
		♀: 4.28	**0.33**
Embryo-fetal development in rats	F_0: 20	370	**30**
	F_1: 5	90.2	**7**
Embryo-fetal development in rabbits	F_0: 25	1010	**79**
	F_1: 25	1010	**79**

ND: not determined

Local Tolerance

Three male New Zealand White rabbits were exposed to 500 mg of encorafenib, 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 post exposure. No skin irritation, corrosion or discoloration was caused by 4 hours exposure to encorafenib.

Other toxicity studies

In vitro phototoxicity study (vh 090801 – non-GLP)

Encorafenib was assayed for phototoxicity to BALB/c 3T3 fibroblast cells using the Neutral Red Uptake assay.

Cells were treated with a range of encorafenib concentrations up to 185.18 μM or the positive control (chlorpromazine). With encorafenib treatment, in the absence of UV-vis light, there was a minimal decrease in cell survival. In the presence of UV-vis light, cytotoxicity was observed at the highest 5 concentrations analysed (1.86 to 185.15 μM). The Photo-Irritation-Factor (PIF) was estimated to be >82. The PIF for the positive control was 33.

2.3.5. Ecotoxicity / environmental risk assessment

Table 14: Summary of main study results

Substance (INN / Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log Pow at pH 4 = 2.5 log Pow at pH 7 = 2.6 log Pow at pH 9 = 1.0	Potential PBT N
PBT-assessment			
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or		0.016μg/L	> 0.01 threshold

refined (e.g. prevalence, literature)					(Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	Sludge Koc = 287.1 – 341.0 $mL.g^{-1}$ Soil Koc = 845.5 – 2 397.2 $mL.g^{-1}$			Adsorption to sludge and soil low
Ready Biodegradability Test	OECD 301	0-2 %, not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT50 (total system) = 203.7-468.6 days DT50 (water) = 19.3-44.4 days DT90 (total system) = 676.8-1 000 days DT90 (water) = 147.5-448.2 days			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	72h-NOEC = 0.75 $mg.L^{-1}$		µg/L	*Pseudokirchneriella subcapitata*, strain: NIVA CHL 1
Daphnia sp. Reproduction Test	OECD 211	21d-NOEC = 0.21 $mg.L^{-1}$		µg/L	Daphnia magna
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	30d-NOEC ≥ 10 $mg.L^{-1}$		µg/L	Zebra fish
Activated Sludge, Respiration Inhibition Test	OECD 209	3h-NOEC = 1000 $mg.L^{-1}$		µg/L	Micro-organisms in activated sludge.
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/kg	
Sediment dwelling organism		NOEC		mg/kg	species

2.3.6. Discussion on non-clinical aspects

In vitro, encorafenib was shown to be a selective ATP-competitive small molecule RAF kinase inhibitor which suppresses the RAF/MEK/ERK pathway in tumour cells expressing BRAFV600E and other muttions (K/D/R) at position V600. The treatment with encorafenib showed that phosphorylated MEK (pMEK) and phosphorylated ERK (pERK) in A375 human melanoma cells was suppressed as well as inhibition of cell proliferation. Encorafenib had no anti-proliferative activity in tumour cell lines that express wild-type BRAF. The primary metabolite, LHY746, was evaluated in in vitro activity studies and was inactive in the inhibition of melanoma cell proliferation. Consequently, in the efficacy and safety studies LHY746 exposure was not assessed.

Tumour regression has been demonstrated in various models at doses as low as 0.6 mg/kg with reproducible and robust effects, including at dose levels of > 3 mg/kg (the absolute exposure (AUC) at the of 5 mg/kg/d is 6.5 µg.h/mL. However, the effect was transient with encorafenib as a single agent and the majority of tumours developed resistance over the course of 4 months of treatment. The combination of encorafenib and binimetinib prevented the emergence of resistant tumours over the 4 month duration of the study resulting in enhanced survival. These data support the hypothesis that combining encorafenib and binimetinib will be efficacious in treating human melanoma.

Safety pharmacology studies were conducted in male rats and monkeys to assess the effects of encorafenib on the cardiovascular, respiratory, and neurobehavioral systems. There were no significant *in vivo* safety findings at doses up to 100 mg/kg in rats.

No preclinical pharmacokinetic studies were performed with encorafenib and binimetinib in combination, this is acceptable as data in clinical studies are deemed more informative.

Secondary pharmacodynamic evaluations showed that encorafenib demonstrated high selectivity for BRAF versus over 143 GPCRs, transporters, ion channels, nuclear receptors and enzymes. Therefore, off-target kinase activity at relevant free-therapeutic concentrations *in vivo* is not anticipated.

The lack of distribution to the CNS is likely due to encorafenib being a P-gp substrate, as P-gp is an important component of the endothelial cell blood-to-brain barrier.

The lack of studies on pharmacodynamics drug interactions, single dose toxicity, carcinogencity and reproduction toxicity are acceptable as per the ICH S9 guideline.

In the 4 week and 13 week rat toxicity studies, clinical signs, reduced body weight reduced epididymides and prostate weights and microscopic findings in testes, epididymides, stomach and skin were noted. Partial reversibility of these findings was noted after a 4 week recovery period. There are no data on the effects of encorafenib on fertility in humans. Based on findings in animals, the use of encorafenib may impact fertility in males of reproductive potential (see section 5.3). As the clinical relevance of this is unknown, male patients should be informed of the potential risk for impaired spermatogenesis. Additionally, in the 13 week rat toxicity study, reversible clinical pathology changes were noted at doses ≥ 100 mg/kg/d. No NOAEL could be established for the 4 week study. The NOAEL for the 13 week study was at 14 to 32 times human therapeutic exposures.

In the 4 week and 13 week monkey toxicity study, isolated/sporadic episodes of emesis and diarrhoea as well as ophthalmic lesions were observed at slightly above human therapeutic exposures. Ophthalmic lesions were partially reversible and consisted of a separation or detachment in the retina between the outer rods and cones layer and retinal pigmented epithelium at the central macula at the fovea. This observation was similar to that described in humans as central serous like chorioretinopathy or central serous retinopathy.

Encorafenib was not genotoxic.

Fertility studies were not conducted with encorafenib. In the sub-acute 28 day and sub chronic 13 week rat toxicology studies, encorafenib treatment at 20 mg/kg/d (dose level approximately 8 times the human exposure at the recommended dose) resulted in decreased testes and epididymis weights with tubular degeneration and oligospermia. In the 13 week study, partial reversibility was noted at the highest dose level (60 mg/kg/d). The embryo-foetal development study in rats indicated that encorafenib induced foetal toxicity with lower foetal weights and delays in skeletal development. A warning on the risk for pregnant women and to the foetus has been included in section 4.6 of the SmPC. Women of childbearing potential must use effective contraception during treatment with encorafenib and for at least 1 month following the last dose. Encorafenib may decrease the efficacy of hormonal contraceptives (see section 4.5). Therefore, female patients using hormonal contraception are advised to use an additional or alternative method such as a barrier method (e.g. condom) during treatment with encorafenib and for at least 1 month following the last dose.

The embryo-foetal development study in rabbits indicated that encorafenib induced foetal toxicity with lower foetal weights and transitory changes in skeletal development. Dilatation of the aortic arc was observed in some foetuses.

It is unknown whether encorafenib or its metabolites 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 encorafenib therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Encorafenib was phototoxic in an in vitro 3T3 Neutral Red Uptake Test. Encorafenib was not a sensitiser in the in vivo mouse sensitization assay. Collectively, these data indicate that encorafenib has a risk of phototoxic potential and minimal risk for sensitization at therapeutic doses in patients.

Encorafenib is not expected to bioaccumulate, or to show any significant transfer to sludge and soil. Therefore, encorafenib is not expected to pose a significant risk to the environment. As for all non-readily biodegradable human medicines, patients should be advised not to dispose of unused encorafenib drug product via wastewater. 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 encorafenib were considered adequate and acceptable for the assessment of non-clinical aspects. The risks to fertility and embryo-foetal development observed in the non-clinical studies have been included in the SmPC. Encorafenib 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 15: Clinical Pharmacology

Study	Objectives	Design	Test Product; Regimen; Route	Number of Subjects	Treatment Duration
Encorafenib					
ARRAY-818-102 Complete; Full	Determine effect of high fat meal on single oral dose PK	Open-label, randomised, single dose, 2-way crossover	Encorafenib capsules (100mg strength); single dose; 2 fed/fasted treatment periods; oral	40 healthy adult subjects	Single dose
ARRAY-162-105 /CMEK162 A2106 Complete; Full	Investigate influence of a PPI (rabeprazole) on binimetinib or encorafenib PK	Fixed sequence, single-centre, open-label, 2- or 3-period crossover study	Binimetinib tablets 3 x 15 mg (45 mg) or encorafenib tablet 1 x 300 mg single dose on Day 1, rabeprazole (20 mg) QD days 4-8; Binimetinib tablets 3 x 15 mg (45 mg) or encorafenib tablet 1 x 100 mg single dose Day 8; Encorafenib tablet 1 x 100 mg single dose on Period 3, Day 1; Oral	15 (Binimetinib) 15 (Encorafenib) Healthy subjects	~6 weeks
CLGX818 A2101 Complete; full	Determine rates and routes of excretion of encorafenib related radioactivity -Determine PK of total radioactivity in blood and in plasma -Characterise plasma PK of encorafenib	Phase 1, single-centre, open-label	[14C]-encorafenib Single 100 mg dose as a micro-emulsion; Oral	4 Healthy male subjects	Single dose
ARRAY-818-101 Ongoing	Evaluate the PK, safety and tolerability of encorafenib following a single 50-mg oral dose of encorafenib in subjects with impaired and normal hepatic function	Phase 1, open-label, multicentre,	Encorafenib single dose 50 mg capsule; Oral	6 subjects with mild hepatic impairment (Child-Pugh Class A) 6 healthy subjects	Single dose

ARRAY-818-105 Complete; Full	Part 1: To determine the effect of multiple oral doses of posaconazole on the single oral dose PK of encorafenib in healthy adult subjects Part 2: To determine the effect of multiple oral doses of diltiazem on the single oral dose PK of encorafenib in healthy adult subjects	Open-label, 2-period, fixed-sequence, 2-part study	Part 1: Encorafenib (50 mg capsules) Posaconazole (40 mg/mL oral suspension); Encorafenib 50 mg QD on Day 1 followed by 400 mg posaconazole BID for 9 days with 50 mg encorafenib QD on Day 7; Oral Part 2: Encorafenib (50 mg capsules) Diltiazem (240 mg capsules); Encorafenib 50 mg QD on Day 1 followed by 240 mg diltiazem QD for 4 days with 50 mg encorafenib QD on Day 2	Part 1: 16 subjects Part 2: 16 subjects Healthy, nontobacco using, adult subjects	Part 1: 9 days Part 2: 4 days
ARRAY-818-103 Ongoing	Evaluate the effects of encorafenib in combination with binimetinib on the PK of losartan, midazolam, caffeine, omeprazole, and dextromethorphan administered in a cocktail approach and on the PK of rosuvastatin in patients with BRAF V600-mutant tumours	Sequential 2-arm, open-label Phase 1 study	Encorafenib (50 mg capsules); Binimetinib (15 mg tablets); CYP probe cocktail (losartan 50mg tablet, midazolam 2 mg/mL oral syrup, caffeine 20 mg/mL oral liquid, omeprazole 20 mg capsule, and dextromethorphan 15 mg capsule) Rosuvastatin 10 mg tablet Arms 1 and 2: Encorafenib 450 mg QD plus binimetinib 45 mg BID on Day 1 Arm 1: CYP probe cocktail (losartan 50 mg, midazolam 2mg, caffeine 100mg, omeprazole 20mg and dextromethorphan 30 mg) on Days -7, 1, and 14 Arm 2: Rosuvastatin 10mg on Days -7, 1 and 14	30 Arm 1: 20 Arm 2: 10 Patients with BRAF V600-mutant unresectable or metastatic melanoma or other advanced solid tumours	14 days

Table 16: Efficacy and Safety

Study Identifier Status Report	Objective(s)	Design	Test Product(s); Dosage Regimen; Route	Number of Subjects	Diagnosis	Treatment Duration
Encorafenib – Initial tolerability						

CLGX818 X2101 Complete Full report	Determine the MTD and/or RP2D of oral encorafenib in adult BRAF V600 mutant patients with locally advanced or metastatic melanoma	Phase 1 multicentre, open-label, dose escalation study of encorafenib in adult patients with locally advanced or metastatic BRAF-mutant melanoma or mCRC	Dose escalation phase: Encorafenib (30 mg/mL micro-emulsion) - 50 and 100 mg QD; Encorafenib (10, 25, 50 & 100 mg capsules) - 50, 100, 150, 200, 300, 450, 550 and 700 mg QD; 75, 100 and 150 mg BID	107 Dose escalation: 54 melanoma patients Dose expansion: 35 melanoma, 18 mCRC patients	Adult patients with locally advanced or metastatic BRAF-mutant melanoma or mCRC	Until progressive disease, unacceptable toxicity or withdrawal of informed consent
Encorafenib and binimetinib – Initial tolerability						
CMEK162 X2110 Complete Full report	Phase 1b: MTD and/or RP2D finding study of encorafenib/ binimetinib & encorafenib/ binimetinib/ ribociclib Phase 2: Efficacy of the dual and triple combination	Multicentre, open-label, dose-finding, Phase 1b dose escalation followed by a Phase 2 efficacy part	Phase 1b: Encorafenib (10, 25, 50 & 100 mg capsules) - 50, 100, 200, 400, 450, 600 or 800mg QD & binimetinib (15mg film-coated tablets) 45mg BID Phase 2: Encorafenib 450 or 600mg QD & binimetinib 45mg BID po	Phase 1b: 47 6: 50 mg 5: 100 mg 4: 200 mg 5: 400 mg 13: 450 mg 8: 600 mg 6: 800 mg (all QD) Phase 2: 79 11 mCRC, 26 prior BRAF inhibitor melanoma, 42 BRAF inhibitor-naïve melanoma	Phase 1b: Patients with BRAF V600 dependent advanced solid tumours Phase 2: Arm 1 – BRAF 600 mutant mCRC Arm 2- metastatic V600 mutant melanoma progressed after prior BRAFi treatment Arm 3 - metastatic V600 mutant melanoma naive to BRAFi treatment	Dual combination until PD, unacceptable toxicity and/ or treatment discontinued at Investigator's discretion or patient refusal
Encorafenib and binimetinib – controlled clinical study						
CMEK162 B2301 Part 1: completed (CSR) Part 2: ongoing	Efficacy/ safety of Combo 450 in BRAF V 600 mutant locally advanced unresectable or metastatic melanoma	Multicentre, randomised, open label, 2 part, phase 3 study comparing efficacy & safety of Combo 450 to vemurafenib and encorafenib monotherapy	Combo 450 arm: encorafenib 450mg QD 7 binimetinib 45mg BID (continuous) Vemurafenib arm: 960mg BID (continuous) Encorafenib arm: 300mg QD (continuous)	Randomised 577 pts: 192 in Combo 450, 194 in encorafenib, 191 in vemurafenib arm	Adult patients (aged ≥18 years) with locally advanced unresectable or metastatic BRAF V600E /V600K-mutant melanoma or unknown primary melanoma (stage IIIB,	Until locally assessed PD confirmed by the BIRC, unacceptable toxicity, death, physician decision, study termination or discontinuation for any other reason (e.g. withdrawal of consent, lost to follow-up)

					IIIC or IV per AJCC)	
Encorafenib / Encorafenib and binimetinib – uncontrolled clinical studies						
CLGX818 X2102 Completed, Full report	Assess anti-tumour activity of encorafenib combined with targeted agents after progression on encorafenib single agent therapy	Phase 2, open label, multicentre, 2-part study	Encorafenib 50 & 100mg capsule strength Part 1 300mg QD Part 2: Encorafenib 450mg OQ + binimetinib 45mg BID	Part 1: 15 patients Part 2: 100 patients (planned) 1 patient	BRAF V600 mutant locally advanced unresectable or metastatic melanoma	Until disease progression, unacceptable toxicity, discontinuation by Investigator or withdrawal of informed consent
CLGX818 X2109 Ongoing Interim CSR on Part 1	Assess the anti-tumour activity, MTD and safety of encorafenib +binimetinib + 3rd targeted agent after progression on encorafenib + binimetinib in BRAF V600 mutant locally advanced unresectable or metastatic melanoma	Multicentre, nonrandomised, open-label, 2-part, Phase 2 study of sequential encorafenib + binimetinib until progression, then rational encorafenib + binimetinib + 3rd targeted agent (based on genetic analysis of tumour biopsy)	Part 1: encorafenib 450mg QD + binimetinib 45mg BID (continuous)	FAS and safety set: 140 (planned), 158 (actual); 75 treatment naïve, 83 non-treatment naïve	Adults with ECOG PS≤2, unresectable stage III or metastatic BRAF V600 mutant melanoma. Part 1: *Group A*: BRAF and MEK inhibitor naïve. *Group B*: progressed post single-agent BRAF or MEK inhibitor or combination (excluding encorafenib, binimetinib), or did not tolerate prior BRAF and/or MEK inhibitor (including encorafenib, binimetinib).	Part 1: Patients treated with encorafenib + binimetinib until progression, unacceptable toxicity, or treatment discontinuation at the Investigator's discretion or by withdrawal of consent. Non-naïve patients treated with encorafenib + binimetinib for ≥ 3 weeks
CLGX818 AUS03 Complete Full report	To assess clinical benefit associated with encorafenib treatment based on local investigator assessment	Phase 2, open-label	Encorafenib 300mg (3 x100mg) QD, continuous dosing with 28 day cycle	12 patients	Solid tumours/ haematological malignancies, pre-identified to have BRAF V600 mutation and disease progression on/ after standard treatment	Until disease progression, unacceptable toxicity, death and/or treatment discontinuation due to any other reasons

2.4.2. Pharmacokinetics

The PK of encorafenib was assessed in 1 clinical study conducted in healthy subjects administered single-agent encorafenib (Study CLGX818A2101), 1 clinical study conducted in advanced cancer patients administered single-agent encorafenib (Study CLGX818X2101) and 3 clinical studies conducted in advanced cancer patients administered encorafenib in combination with binimetinib (Studies CMEK162X2110, CGLX818X2109 and CMEK162B2301).

Absorption

Because encorafenib demonstratesd high apparent permeability and its solubility in media with higher pH, encorafenib was designated as a BCS Class II drug.

In the clinical ADME study CLGX818A2101, 4 healthy subjects received a single oral dose of 100 mg [14C]-encorafenib. The extent of oral absorption was estimated to be at least ~86% based on a mean of 47.2% of the radioactivity dose eliminated in the urine and 39% of the radioactivity dose recovered in the faeces as metabolites.

After oral administration, encorafenib is rapidly absorbed with a median T_{max} of 1.5 to 2 hours.

Table 17: Summary statistics of plasma PK parameters for encorafenib (PAS) - Study CLGX818A2101

Statistics	AUCinf (ng*hr/mL)	AUClast (ng*hr/mL)	AUC0-24 (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	CL/F (L/hr)	Vz/F (L)
n	4	4	4	4	4	4	4	4
Mean (SD)	3940 (1430)	3910 (1450)	3850 (1370)	1050 (171)	N/A	6.11 (1.84)	27.9 (9.15)	235 (73.7)
CV% mean	36.4	37.0	35.6	16.3	N/A	30.0	32.8	31.4
Geo-mean	3750	3720	3680	1040	N/A	5.88	26.6	226
CV% geo-mean	36.3	37.1	35.7	17.3	N/A	34.0	36.3	32.7
Median	3610	3600	3570	1080	0.767	6.32	28.4	228
[Min-Max]	[2660-5860]	[2600-5840]	[2600-5670]	[820; 1230]	[0.500; 1.00]	[3.74; 8.09]	[17.1; 37.6]	[168; 316]

- n: number of subjects with non-missing values.
- CV% = coefficient of variation (%) = SD/mean*100, CV% geo-mean = sqrt(exp(variance for log transformed data)-1)*100.
- For Tmax only n, median and range are presented.

Influence of food

The effect of food on encorafenib PK was evaluated in Study ARRAY-818-102.

The administration of a single oral 100 mg dose of encorafenib with food resulted in no significant change in total exposure (i.e., AUC) following a High Fat Meal (HFM); however, the rate of absorption for encorafenib was slower in the fed state, as evidenced by an approximate 2.3-hour delay in the time to maximum observed plasma concentration (i.e., Tmax) and a lower peak concentration (i.e., 340.5 ng/mL lower Cmax) in the fed state.

The AUCinf decreased by approximately 4% after administration of a HFM (GMR=95.91%); however, the treatment groups were bioequivalent in terms of the AUCinf as indicated by the 90% CI of the GMR (91.62, 100.39).

Peak exposure (i.e., Cmax) decreased by approximately 36% (GMR=63.97%) and this change was found to be statistically significant as indicated by the 90% CI of the GMR for Cmax (57.73, 70.90). The non-parametric median differences in Tmax (2.253 [90% CI 2.002, 2.516]) were also found to be statistically significant ($p < 0.0001$) between the 2 treatments.

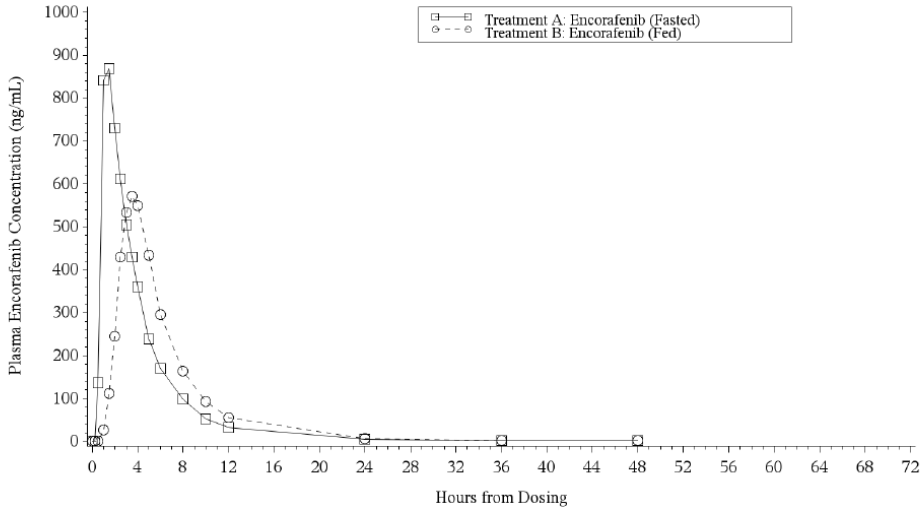


Figure 8: Mean plasma concentration-time profiles of encorafenib following administration of a single oral dose of 100 mg encorafenib under fasted and fed conditions

Table 18: Plasma Encorafenib Pharmacokinetic Parameters Following Administration of a Single Oral Dose of 100 mg Encorafenib Under Fasted and Fed Conditions

Treatment[a]	Statistic[b]	$AUC_{0\text{-inf}}$ (ng.h/mL)	C_{max} (ng/mL)	T_{max} (h)
Encorafenib (Fasted) (100 mg)	n	30	31	31
	Geo-mean	3121	961.5	-
	Geo-CV (%)	42.3	32.9	-
	Median	-	-	1.495
	Min	-	-	0.997
	Max	-	-	3.49
Encorafenib (Fed) (100 mg)	n	31	31	31
	Geo-mean	3034	621.0	-
	Geo-CV (%)	38.4	45.2	-
	Median	-	-	3.499
	Min	-	-	2.00
	Max	-	-	5.00

Distribution

In the human ADME study, the mean blood-to-plasma concentration ratio for total radioactivity was 0.58.

The in vitro mean plasma protein binding of encorafenib was approximately 86.1% over the concentration range of 50 to 50,000 ng/mL. The in vitro mean protein binding for AR00492720 (encorafenib metabolite) was 95.8, 89.6 and 88.6 in rat, monkey and human plasma, respectively.

The geometric mean (% CV) Vz/F for encorafenib was 226 L (32.7%).

Based on the population PK analysis, the typical initial distribution half-life into the second compartment of the population PK model was 0.34 hours and the total volume of the central compartment (V/F) was 27 L.

Elimination

In the ADME study, 4 healthy subjects received a single oral dose of 100 mg [14C]-encorafenib. The plasma encorafenib concentrations exhibited a biphasic elimination. The extent of oral absorption was estimated to be at least ~86% based on a mean of 47.2% of the radioactivity dose eliminated in the urine and 39% of the radioactivity dose recovered in the faeces as metabolites.

The percentage of the dose eliminated in the urine as unchanged encorafenib was approximately 1.8% of the apparent total clearance after oral administration (CL/F). The estimated mean encorafenib renal clearance (CLr) was 0.5 L/h and was 7% of the glomerular filtration rate (7.5 L/h), suggesting minimal involvement of renal transporters in its elimination process. The percentage of the dose eliminated in the faeces as unchanged encorafenib was also minor with a mean of 5.0%.

Therefore, metabolism was found to be the major clearance pathway (~88% of the recovered radioactive dose) for encorafenib in humans.

In the same study, the median (range) t1/2 for encorafenib was 6.32 hours (3.74 to 8.09 hours). The geometric mean (% CV) CL/F and apparent volume of distribution following oral administration (Vz/F) were 26.6 L (36.3%) and approximately 226 L (32.7%), respectively.

Based on the population PK analysis, the population estimate of CL/F for encorafenib was 27.9 L/h. The elimination t1/2 derived with the model was 12.1 h.

In the ADME study in human, metabolism was found to be the major clearance pathway (~88% of the recovered radioactive dose) for encorafenib in humans, leading to an estimated level of oral absorption of at least ~86%.

Dose proportionality and time dependencies

The dose proportionality for encorafenib was assessed for $AUC_{T,ss}$ and $C_{max,ss}$ over pooled dose ranges of 50 to 800 mg and 50 to 600 mg.

Encorafenib was rapidly absorbed with a median Tmax that ranged from 0.50 to 2.50 hours across doses. Plasma AUCs and Cmax of encorafenib increased in a slightly less than dose-proportional manner as the encorafenib dose increased from 50 to 800 mg on Day 15. Encorafenib concentrations rapidly declined and the geometric mean t1/2 was similar across doses (ranging from 2.88 to 4.63 hours).

Accumulation of encorafenib was also assessed with an ANOVA performed on log-transformed AUCtau,ss and Cmax,ss using an LME model with day (Day 15 versus Day 1) as a fixed effect and subject as a random

effect. The estimated ratios for Cmax (RCmax) and for AUC (RAUC) were 0.63 and 0.45, respectively, which is consistent with the effect of auto-induction of CYP3A4. The intra-subject variability was approximately 37.36% and 36.40%, respectively.

The typical CL/F of encorafenib was estimated to be 34% faster after Cycle 1 Day 1. An Emax function was used to describe time-dependent behaviour for the CL/F of encorafenib during the treatment, with 50% of the maximum CL/F (T50) achieved at 18.33 hours after the 1st administration.

Table 19: Encorafenib pharmacokinetic parameters on Cycle 1 Day 1 – Study CLGX818X2101

Dose and Regimen (N)	Pharmacokinetic Parameter on Day 1[a]					
Parameter Unit	C_{max}[b] (ng/mL)	T_{max}[c] (h)	AUC_{tau}[b] (ng.h/mL)	$T_{1/2}$ (h)	CL/F[b] (L/h)	V_z/F[b] (L)
50 mg QD (1)	970 (NC)	2 (2, 2)	5360 (NC)	4.38 (4.38, 4.38)	9.14 (NC)	57.8 (NC)
100 mg QD (5)	1630 (42.4)	2 (0.5, 2)	7610 (83)	3.47 (3.38, 3.88)	13 (83.4)	67 (79.4)
150 mg QD (6)	1570 (28.8)	2 (0.52, 4.0)	9400 (20.1)	3.66 (3.09, 4.5)	15.8 (20.1)	84.5 (28.2)
200 mg QD (4)	1850 (28.1)	2 (2, 2)	9860 (26.5)	3.3 (2.56, 3.58)	20.2 (26.2)	91.9 (39.6)
300 mg QD (5)	3310 (42.5)	2 (2, 8)	20300 (29.1)	3.42 (2.84, 4.77)	15 (33.4)	76.5 (33.7)
450 mg QD (6)	5970 (56.4)	2 (2, 2.3)	32800 (69.1)	2.92 (2.32, 4.98)	13.6 (70.3)	60.5 (53.3)
550 mg QD (5)	5360 (36.9)	2 (2, 2.07)	31700 (45.3)	3.32 (3.28, 3.61)	17.2 (45.5)	84.8 (42.0)

Table 20: Encorafenib 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 CLGX818X2101 Encorafenib Single Agent						
50 mg Encorafenib QD (N=1)	465 (NC)	2 (2, 2)	2660 (NC)	0.496 (NC)	18.8 (NC)	112 (NC)
100 mg Encorafenib QD (N=5)	959 (25.19)	2.99 (2, 4)	5330 (36.58)	0.535 (21.08)	18.8 (36.58)	103 (36.42)
150 mg Encorafenib QD (N=6)	1300 (29.08)	2 (0.5, 2.03)	4750 (12.25)	0.476 (20.79)	31.5 (12.25)	188 (43.23)
200 mg Encorafenib QD (N=4)	1300 (31.12)	2 (2, 2.17)	5060 (35.79)	0.468 (19.72)	39.5 (35.79)	177 (31)
300 mg Encorafenib QD (N=5)	2920 (34.41)	2 (2, 2.02)	10100 (53.35)	0.541 (73.21)	29.6 (53.35)	128 (12.49)
450 mg Encorafenib (N=6)	3950 (49.12)	2 (0.5, 2)	13100 (34.85)	0.401 (51.64)	34.3 (34.85)	157 (38.55)
550 mg Encorafenib QD (N=5)	4170 (48.94)	2 (2, 2)	15300 (36.38)	0.468 (59.74)	36 (36.38)	221 (75.92)

Population PK

The final population PK model of encorafenib consisted of a 2-compartment model with time varying clearance. The absorption of encorafenib was described with a first-order rate of absorption.

The population estimates of CL/F and V/F for encorafenib were 27.9 L/h and 14.1 L, respectively. The t1/2 derived with the model was 12.1 h. Total volume of distribution was 27.3 L.

Table 21: Final Population PK Model of Encorafenib (Enco 06) – Typical Value

Parameters	Fixed Effects		Random effects		
	Estimate	Unit	Variance	IIV%	Shrinkage
Ka	0.357	h^{-1}	0.008	8.93%	38.33%
V/F	14.106	L	1.646	128.29%	20.91%
V2/F	13.197	L	0.187	43.26%	73.97%
CL/F	27.863	L/h	0.103	32.13%	29.27%
CL2/F	0.779	L/h	0.204	45.16%	77.69%
Tlag	0.446	h			
T50 (h)	18.33 (fixed)	h			
Emax	-0.340	h^{-1}	1.034	101.67%	72.81%
Stdev0 (additive error on ln-transformed)	0.986				
		Multiplicative factor			
WT effect on CL/F - $(WT/75)^{\theta}$	0.270				
WT effect on V/F - $(WT/75)^{\theta}$	0.850				
Disease effect on CL/F - exp(θ)	-0.121	×0.886			
Age on V/F - $(Age/53)^{\theta}$	-0.125				
Total proteins on CL/F - $(TPROT/70)^{\theta}$	0.058				
Bilirubin on CL/F - $(BIL/0.4678)^{\theta}$	-0.137				
Moderate Inhibitor on CL/F- exp(θ)	-0.205	×0.815			
Strong Inhibitor on CL/F - exp(θ)	-0.170	×0.844			
LDH on CL/F - $(LDH/327)^{\theta}$	-0.030				
ECOG on CL/F - exp(θ *(ECOG=1))	-0.100	×0.905			
ECOG on CL/F - exp(θ *(ECOG=2))	-0.165	×0.848			
eGFR on CL/F - $(eGFR/111.6)^{\theta}$	0.064				

BIL= Bilirubin (mg/dL); CL/F= Apparent clearance; CL2/F= Apparent inter-compartmental clearance; ECOG= Eastern Cooperative Oncology Group status; eGFR= Estimated glomerular filtration rate (mL/min/1.73m^2); Emax= Maximum effect; IIV%= Inter-individual variability; LDH = Lactate dehydrogenase (U/L); Stdev0= Standard deviation of log-additive error; t= Time (h); T50= Time to reach the maximum effect; Tlag= Lag time of absorption; TPROT= Total protein (g/L); V/F= Apparent central volume of distribution; V2/F= Apparent peripheral volume of distribution; θ= Covariate effect; WT= Body weight (kg)
Note : Time effect on CL/F was implemented using the following equation : 1-Emax*t/(T50+t))

Special populations

Renal impairment

The applicant did not submit studies in renal impaired patients. However, the effect of the mild and moderate renal impairment on the PK of encorafenib was evaluated using a population PK approach. In a population pharmacokinetic analysis, no clear trend in encorafenib CL/F was observed in patients with mild (eGFR 60 to 90 mL/min/1.73 m2) or moderate (eGFR 30 to 59 mL/min/1.73 m2) renal impairment compared with subjects with normal renal function (eGFR ≥90 mL/min/1.73 m2). A small decrease in CL/F (≤5%) was predicted for patients with mild and moderate renal impairment, which is unlikely to be clinically relevant.

Hepatic impairment

The pharmacokinetics of 50 mg encorafenib was investigated in mild hepatic impairment subjects versus healthy subjects. Healthy subjects were enrolled based on matched age, gender and body weight to a hepatic impaired subject and could have matched more than one subject in a different impairment group. The lowest possible dose of 50 mg encorafenib was administered in this study. After review of the safety and PK data, a total of 6 subjects with mild hepatic impairment and 6 matching healthy subjects were dosed. Results from this cohort indicated an approximate 25% increase in overall encorafenib exposure (AUCinf) in subjects with mild hepatic impairment compared with matching healthy subjects. Considering the unbound encorafenib fraction, Cmax was increased by 21%, AUC increased by 55% and Cl/F reduced by 36%.

Table 22: Geometric mean (geometric coefficient of variation) plasma pharmacokinetic parameters for encorafenib and unbound encorafenib

Parameter	Encorafenib		Unbound Encorafenib	
	Healthy	Child-Pugh A	Healthy	Child-Pugh A
Cmax (ng/mL)	494 (31.4)	484 (26.6)	33.5 (32.8)	40.7 (24.9)
Tmax (h)[a]	1.50 (1.00, 3.00)	1.50 (1.00-2.00)	NA	NA
AUC0-inf (h.ng/mL)	1990 (29.5)	2490 (47.1)	135 (26.8)	209 (48.5)
Cl/F (L/h)	25.2 (29.5)	20.1 (47.1)	371 (26.8)	239 (48.5)
Fu (%)	6.77 (9.1)	8.40 (4.9)	NA	NA

Abbreviations: MA, not applicable

[a] Median (minimum, maximum) values are presented for Tmax

FU: fraction of encorafenib unbound.

In the population PK analysis, the covariate of hepatic impairment indicated no significant impact on the encorafenib CL/F or V/F when comparing healthy subjects with mild hepatic impairment subjects. Information on unbound encorafenib fraction (6.77%) from the healthy volunteers obtained in the HI study ARRAY-818-101 was included to predict AUC and Cmax and was also compared with predicted values based on previous in vitro FU values (13.9%).

The model predicted an unbound encorafenib fraction for subjects with Child-Pugh A of 8.17% (ex vivo value measured in the clinical HI study was 8.4%.

Gender

Based on the results of the population PK modelling, gender was not retained as a covariate in the final model for encorafenib.

Race

Based on the results of the population PK modelling, no apparent trend for V/F and race or ethnic origin was observed in the exploratory plots.

Weight

Based on the results of the population PK modelling, for an individual in the 95th percentile of weight (i.e. 112 kg), the population PK analysis indicated a 11.4% increase in CL/F compared to the typical individual of 78 kg. For an individual in the 5th percentile of weight (i.e. 54 kg), the population PK analysis indicated an 8.5% decrease in CL/F compared to the typical individual of 75 kg. The exponent for weight on clearance in the POPPK model was 0.27.

Elderly

Age as a covariate was not retained in the final model on the CL/F term.

		CL/F (L/h)				V/F (L)			
Study	**Age category**	**65 - 74 years**	**75 - 84 years**	**85+ years**	**Adults**	**65 - 74 years**	**75 - 84 years**	**85+ years**	**Adults**
All studies	NObs	201	70	7	749	201	70	7	749
	Mean	23.4	23.7	24.1	26.5	22.7	25	58	31.2
	CV%	24	22.5	41.6	25.5	180	164	203	164
	Min	7.42	9.41	14.8	7.49	0.662	1.55	2.44	0.626
	Median	22.7	23.6	22.8	25.9	10.7	13.3	14.7	13.7
	Max	49.9	43.9	45.2	51.5	428	213	323	682

Nobs: number of values na : not applicable ; CL/F : Apparent Clearance ; V/F : Apparent central volume of distribution ;

Pharmacokinetic interaction studies

The available data suggest that CYP3A4 is the primary enzyme likely to cause a clinical DDI. CYP3A4 is the major enzyme contributing to total oxidative clearance of encorafenib in human liver microsomes (~83.3%), followed by CYP2C19 and CYP2D6 (~16.0% and 0.71%, respectively), with CYP2C19 being the major contributor (70.1%) to the oxidative metabolism of AR0049272.

Given that encorafenib is a substrate of both CYP3A4 and P-glycoprotein (P-gp), the effect of both CYP3A4 and P-gp transporter inhibitors on encorafenib exposure was evaluated. Based on the results of the PBPK analysis, encorafenib can be classified as low-to-moderate passive permeability compound when P-gp is not saturated/inhibited and as high passive permeability compound in presence of P-gp inhibitor or at encorafenib concentrations higher than 164 µM. Encorafenib exhibited potential inhibition of P-gp transportation in vitro at concentrations up to 1000 µM, with a calculated Ki ~75µM. This is much lower than the calculated gut concentrations and the PBPK model predicted local concentrations of 5 mM.

The predicted DDI effect for ketoconazole and itraconazole were approximately 5-fold and could be classified as moderate-to-strong.

Co-administration of posaconazole (a strong CYP3A4 inhibitor) increased the overall encorafenib exposure (i.e., AUC) by approximately 3-fold when a multiple dose of posaconazole was co-administered with a single dose of encorafenib 50 mg in healthy subjects. Based on the predicted DDI using higher dose of posaconazole at the steady state, a similar effect of posaconazole on the PK of encorafenib was observed.

Similarly, co-administration of diltiazem (a moderate CYP3A4 inhibitor and P-gp transporter inhibitor) increased the overall encorafenib exposure by approximately 2-fold. The Tmax values were similar.

Encorafenib appears to inhibit hepatic uptake transporters OCT1, OATP1B1 and OATP1B3, renal uptake OAT1, OAT3 and OCT2 and BCRP transporter involved in efflux in the gut, liver and kidney.

The DDI module in GastroPlus™ v. 9.0 was used to run dynamic simulations to predict the extent of DDIs between ketoconazole (KET) or itraconazole (ITZ) and CYP3A4 substrates midazolam (MID), triazolam (TRZ), and quinidine (QND) using PBPK models. The full itraconazole model overpredicted the DDI effect in four studies (ratio of predicted/observed RAUC values ranging from 1.06 to 1.51) and underpredicted the DDI effect in the eight remaining studies (ratio of predicted/observed RAUC values ranging from 0.42 to 0.88). In clinical studies the observed effect of itraconazole on midazolam PK ranged from 3 to 11-fold increase in AUC and the model predicted a range of 2 to 8-fold. For triazolam, the observed effects of itraconazole ranged from 2 to 5-fold increases in AUC and the model predicts a slightly lower range of 1.2 to 4-fold. For quinidine the observed 2-fold increase in AUC, when co-administered with itraconazole was well predicted by the model (1.7 fold).

The ketoconazole model was evaluated by predicting the DDI effect with MID and TRZ from two different studies. The ratio of predicted/observed RAUC was 0.96 and 0.79, respectively. Predictions of inhibition effect of posaconazole, ketoconazole, and itraconazole on encorafenib PK in patients on day 1 and day 7 after coadministration of encorafenib and inhibitor for 7 days were performed and are shown in Table 23.

Table 23: Predicted effect of CYP3A4 inhibitors on encorafenib exposures in cancer patients

Encorafenib dose	CYP3A4 inhibitor (dose)	Category	Day 1		Steady state	
			R_{Cmax}	R_{AUC}[b]	R_{Cmax}	R_{AUC}
300 mg QD	Posaconazole (400 mg BID)	Strong	2.33	2.49	2.90	3.12
	Ketoconazole (400 mg QD)	Strong	3.05	4.58	4.01	5.83
	ITZ-full (200 mg QD)[c]	Strong	2.69	3.27	3.61	4.98
450 mg QD	Posaconazole (400 mg BID)	Strong	2.14	2.30	2.66	2.89
	Ketoconazole (400 mg QD)	Strong	2.79	4.23	3.68	5.42
	ITZ-full (200 mg QD)	Strong	2.47	3.02	3.31	4.63

[a] The encorafenib model was for a 59.3 year-old male cancer patient that weighed 79.8 kg. The R values presented here are a comparison of encorafenib exposure with a CYP3A4 inhibitor compared to encorafenib exposure without a CYP3A4 inhibitor both on Day 1 and on Day 7, considered to be at steady state.
[b] Calculated based on AUC(0-t) with t = 24 hr.
[c] ITZ-full refers to itraconazole PBPK model with three metabolites (OH-ITZ, Keto-ITZ, and ND-ITZ)

Pharmacokinetics using human biomaterials

See section on metabolism.

2.4.3. Pharmacodynamics

Mechanism of action

See non-clinical section.

Primary and Secondary pharmacology

Cardiac safety

A post hoc analysis of Phase 1 Study CLGX818X2101 was conducted to evaluate the potential for therapeutic concentrations of encorafenib to cause QT prolongation (Report **CP17-005**). An increase in ΔQTcF from Baseline of >30ms was observed in 47 out of 105 evaluable patients (44.8%) and an increase in QTcF >60ms was observed in 5 patients (4.8%). A new QTcF >480ms occurred in 2 patients (1.9%); no new QTcF >500ms were observed.

The datasets included 77 subjects and 1002 time-matched ECG-concentration pairs for encorafenib and were analysed with a linear mixed effects (LME) model. In the central tendency analysis for the 450mg dose group, the mean ΔQTcF (upper bound two-sided 90% CI) at 2 hours post-dose (T_{max}) was 12.7ms (16.2ms) on Day 1 and 19.9ms (26.5ms) on Day 15. For the 300mg dose group, the mean ΔQTcF (upper bound two-sided 90% CI) at 2 hours post-dose (T_{max}) was 5.2ms (9.2ms) on Day 1 and 12.9ms (19.0ms) on Day 15. In the escalation phase, the mean maximum postbaseline ΔQTcF across patients at the 300mg dose was 26.2msec (90% CI = 7.8 to 44.6) and 24.9msec (90% CI = 20.2 to 29.7 msec) at the 450mg dose. In the expansion phase, the mean maximum postbaseline ΔQTcF across patients at the 300mg dose was 30.9msec (90% CI = 24.8 to 37.0 msec) and 33.4msec (90% CI = 28.0 to 38.8 msec) at the 450mg dose.

Exposure-safety relationship

Exposure safety (E-S) analysis was conducted based on 4 clinical studies using logistic regression to model predicted AUCss and the expected incidence of selected adverse events, specifically all-grade ALT, and ≥ grade 2 PPE, pyrexia and diarrhoea. In general, the predicted exposure-safety relationships for both substances were similar in combination due to mutual confounding effects.

However, when the encorafenib dose was fixed, higher AUCss of binimetinib resulted in a higher probability of ALT increase relative to encorafenib monotherapy, although not statistically significant.

The probability of PPED was up to 44% for encorafenib monotherapy and the encorafenib effect was attenuated by binimetinib co-administration. Higher binimetinib exposure as indicated by AUCss, Cmaxss and Cminss was associated with lower probability of PPED.

The applicant conducted additional exposure-safety analyses using the updated popPK model; these were 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). Increasing encorafenib exposure in mono-and combination treatment was associated with an increased probability of elevated CK (all grades) and a reduced probability of skin infection.

Exposure-efficacy relationship

Kaplan-Meier plots of PFS (time-to-event) were derived by high/low exposure (relative to the median) and by quartiles of AUCss, Cmax,ss, and Cmin,ss for encorafenib and binimetinib based on the randomised dose.

Encorafenib monotherapy showed a similar median PFS between patients with higher and lower encorafenib exposure (PFS of 9.56 and 9.33 months respectively). PFS was higher in the Combo 450 arm but patients with high encorafenib exposure showed lower PFS compared to patients with lower encorafenib exposure (11.0 and 18.0 months, respectively). On review, patients with higher encorafenib exposure in the Combo 450 arm had poorer prognostic factors, particularly an increased proportion with LDH above the median. The

median PFS time in patients with baseline LDH below and above the median were 21.9 and 9.0 months, respectively.

The logistic regression models for ORR and Cox hazard models for PFS were updated and results for Combo and encorafenib monotherapy treatments were presented for Part 1 and Part 2 and both parts combined, although only limited analyses involving encorafenib monotherapy from Part 2 alone were presented. The median PFS with encorafenib monotherapy was shorter in Part 2 (7.36 months) than Part 1 (9.56 months).

7.24 Kaplan-Meier Curves of PFS – Stratification by Encorafenib AUCss Lower and Higher than Median (Combo450)

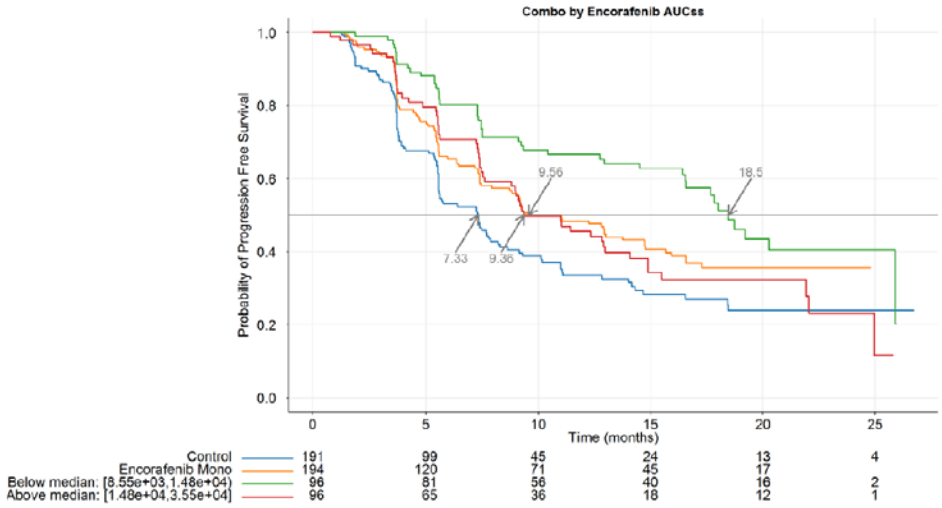


Figure 9: PFS Stratified by Encorafenib AUCss Above and Below the Median in Combo 450 (Part 1)

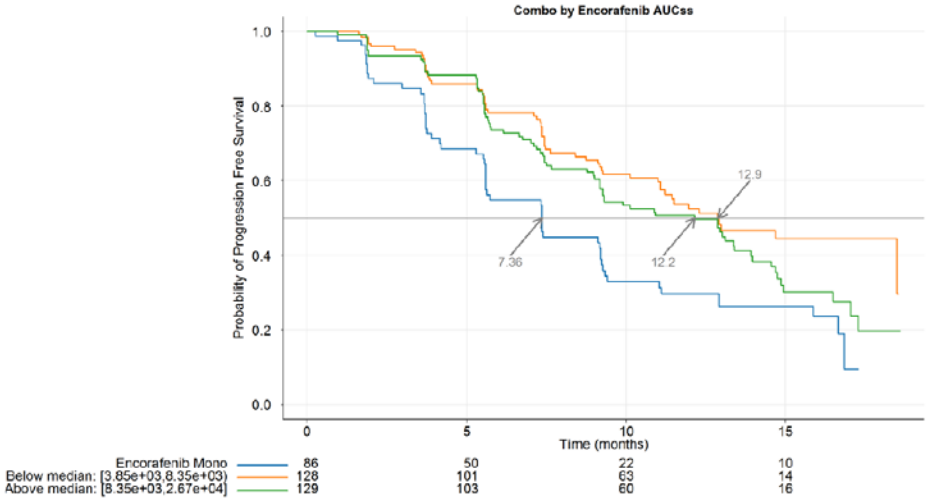


Figure 10: PFS Stratified by Encorafenib AUCss Above and Below the Median in Combo 300 (Part 2)

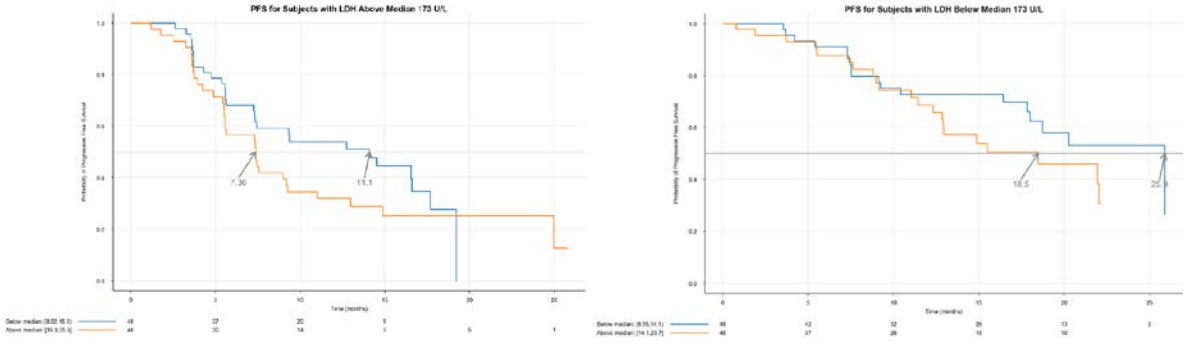


Figure 11: Part1 - Combo450 – stratification of PFS by encorafenib AUC and LDH
Left: For patients with high LDH (>173 U/L) median AUC is calculated with 15.3 µg*h/ml
Right: For patients with low LDH median AUC is calculated with 14.1 µg*h/ml

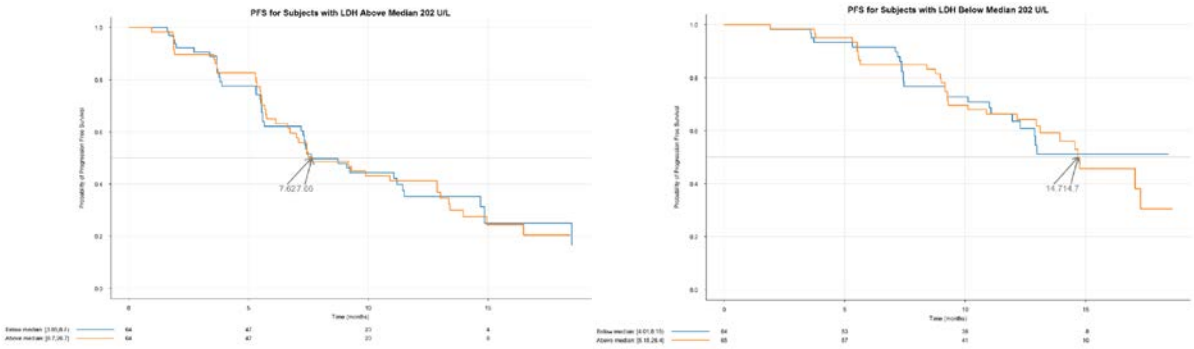


Figure 12: Part 2 - Combo300 – stratification of PFS by encorafenib AUC and LDH
Left: For patients with high LDH (>202 U/L) median AUC is calculated with 6.7 µg*h/ml
Right: For patients with low LDH median AUC is calculated with 8.15 µg*h/ml

The applicant re-evaluated the Cox proportional hazard models for Part 2 and Part 1 and 2 combined utilising "corrected" median AUC values. A significant positive treatment effect as a function of encorafenib exposure (AUCss) was not established.

Graphs of the probability of PFS according to encorafenib exposure (AUCss) were provided for Combo 450, Combo 300, Enco 300 Part 1 and Enco 300 Part 2 in the D180 responses. Also, graphs of probability of ORR and PFS by encorafenib Cmin were provided for these different populations. There was no clear relationship between Cminss of encorafenib and PFS or ORR in Part 1 or Part 2 of the COLOMBUS study for single agent encorafenib or in combination with binimetinib. It was not possible to establish a target Cmin,ss or Ctrough for encorafenib in order to guide dosing. No consistent relationship was observed between AUCss and PFS. The only trend (although not statistically significant) was a decrease in PFS with increased encorafenib AUCss with Combo450 in Part 1, as noted previously. This could have arisen by chance, due to higher baseline LDH levels or be the result of interaction with an unidentified covariate/ confounding factor. Patients with higher baseline LDH levels still had a positive treatment effect with Combo450 compared to vemurafenib in terms of PFS; however, this was not statistically significant with the confidence interval crossing 1 [PFS Combo 450 vs. vemurafenib: high LDH HR 0.73 (95% CI 0.47, 1.14); low LDH HR 0.47 (95% CI 0.33, 0.67)].

2.4.4. Discussion on clinical pharmacology

The pharmacokinetics of encorafenib were studied in healthy subjects and patients with solid tumours, including advanced and unresectable or metastatic cutaneous melanoma harbouring a BRAF V600E or K mutation. The pharmacokinetics of encorafenib have been shown to be approximatively dose linear after single and multiples doses. After repeat once-daily dosing, steady state conditions were reached within 15 days. The accumulation ratio of approximately 0.5 is likely due to auto induction of CYP3A4. The inter subject variability (CV%) of AUC is ranged from 12.3% to 68.9%.

Encorafenib is moderately (86.1%) bound to human plasma proteins *in vitro*. Following a single oral dose of 100 mg [^{14}C] encorafenib in healthy subjects, the mean (SD) blood-to-plasma concentration ratio is 0.58 (0.02) and the mean (CV%) apparent volume of distribution (Vz/F) of encorafenib is 226 L (32.7%).

After oral administration, encorafenib is rapidly absorbed with a median Tmax of 1.5 to 2 hours. Following a single oral dose of 100 mg [14C] encorafenib in healthy subjects, at least 86% of the encorafenib dose was absorbed. Administration of a single 100 mg dose of encorafenib with a high-fat, high-calorie meal decreased the Cmax by 36%, while the AUC was unchanged. A drug interaction study in healthy subjects indicated the extent of encorafenib exposure was not altered in the presence of a gastric pH-altering agent (rabeprazole).

Following a single oral dose of 100 mg [^{14}C] encorafenib in healthy subjects, metabolism was found to be the major clearance pathway for encorafenib (approximately 88% of the recovered radioactive dose). The predominant biotransformation reaction of encorafenib was N-dealkylation. Other major metabolic pathways involved hydroxylation, carbamate hydrolysis, indirect glucuronidation and glucose conjugate formation.

Following a single oral dose of 100 mg [^{14}C] encorafenib in healthy subjects, radioactivity was eliminated equally in both the faeces and urine (mean of 47.2%). In urine, 1.8% of the radioactivity was excreted as encorafenib. The mean (CV%) apparent clearance (CL/F) of encorafenib was 27.9 L/h (9.15%). The median (range) encorafenib terminal half-life ($T_{1/2}$) was 6.32 h (3.74 to 8.09 h).

For dose modifications see Table 1 of the SmPC. Administration of encorafenib at a dose of 450 mg once daily as a single agent is not recommended. If binimetinib is temporarily interrupted, encorafenib should be reduced at 300 mg once daily during the time of binimetinib dose interruption (see section 4.2 of binimetinib Summary of Product Characteristics [SmPC]) 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 Table 2), binimetinib should be interrupted. If encorafenib is permanently discontinued, then binimetinib should be discontinued.

Effect of CYP enzymes on encorafenib

Encorafenib is metabolised by CYP3A4, CYP2C19 and CYP2D6. *In vitro*, CYP3A4 was predicted to be the major enzyme contributing to total oxidative clearance of encorafenib in human liver microsomes (~83.3%), followed by CYP2C19 and CYP2D6 (~16.0% and 0.71%, respectively).

Encorafenib is primarily metabolised by CYP3A4. Stronger CYP3A4 inhibitors (e.g. posaconazole, ketoconazole, itraconazole) are expected to have moderate to strong effects on encorafenib exposure. Moderate CYP3A4 inhibitor and P-gp transporter inhibitor (e.g diltiazem) are expected to moderately increase the overall encorafenib exposure (approximately 2-fold). Concomitant treatment of encorafenib with strong

CYP3A4 inhibitors should be avoided and co-administration with moderate inhibitors should be considered with caution. See section 4.5 of the SmPC for information on effect of CYP3A4 inhibitors and inducers on encorafenib exposure.

Effect of encorafenib on CYP substrates

In vitro experiments indicate encorafenib is a relatively potent reversible inhibitor of UGT1A1, CYP2B6, CYP2C9 and CYP3A4/5, as well as a time-dependent inhibitor of CYP3A4. Encorafenib induced CYP1A2, CYP2B6, CYP2C9 and CYP3A4 in human primary hepatocytes. Simulations of 450 mg encorafenib co-administered with probe substrates for CYP2B6, CYP1A2, CYP2C9, CYP2C19 and CYP2D6 on Day 1 and Day 15 all indicated no clinically relevant interactions are expected. For co-administration with CYP3A4 and UGT1A1 substrates that undergo gut extraction, a minor to moderate interaction is expected. While binimetinib is a UGT1A1 substrate, it does not undergo gut extraction and therefore no DDI with encorafenib is expected. Additionally, no differences in exposure have been observed clinically when binimetinib is co-administered with encorafenib.

Encorafenib is both an inhibitor and inducer of CYP3A4. Concomitant use with agents that are substrates of CYP3A4 (e.g., hormonal contraceptives) may result in increased toxicity or loss of efficacy of these agents. Women of childbearing potential must use effective contraception during treatment with encorafenib and for at least 1 month following the last dose. Encorafenib may decrease the efficacy of hormonal contraceptives (see SmPC section 4.5). Therefore, female patients using hormonal contraception are advised to use an additional or alternative method such as a barrier method (e.g. condom) during treatment with encorafenib and for at least 1 month following the last dose.

Concurrent use of strong CYP3A inhibitors during treatment with encorafenib should be avoided. If concomitant use with a strong CYP3A inhibitor is necessary, patients should be carefully monitored for safety (see section 4.5). Caution should be exercised if a moderate CYP3A inhibitor is co-administered with encorafenib.

Agents that are CYP3A4 substrates should be co-administered with caution.

Encorafenib is an inhibitor of UGT1A1. Concomitant agents that are substrates of UGT1A1 (e.g. raltegravir, atorvastatin, dolutegravir) may have increased exposure and should be therefore administered with caution.

Effect of transporters on encorafenib

Encorafenib was found to be a substrate of the P-glycoprotein (P-gp) transporters. Inhibition of P-gp is unlikely to result in a clinically important increase in encorafenib concentrations as encorafenib exhibits high intrinsic permeability. The involvement of several uptake transporter families (OCT1, OATP1B1, OATP1B3 and OATPB1) was investigated *in vitro* using relevant transporter inhibitors. The data suggest that hepatic uptake transporters are not involved in encorafenib distribution into primary human hepatocytes.

Effect of encorafenib on transporters

In vitro, encorafenib inhibited the hepatic transporter OCT1, but is unlikely to be an effective inhibitor clinically. Based on *in vitro* studies, there is potential for encorafenib to inhibit renal transporters OCT2, OAT1, OAT3 and hepatic transporters OATP1B1 and OATP1B3 at clinical concentrations. In addition, encorafenib may inhibit P-gp in the gut and BCRP at the expected clinical concentrations.

Encorafenib should be therefore co-administered with caution. (SmPC section 4.6)

For special populations, in contrast to gender, age and body weight were found to be signifcant covariates for volume distribution. However it is unlikely they have a clinically relevant effect and no dose adjustments are needed. (SmPC section 4.2 and 5.3). There are insufficient data to evaluate potential differences in the exposure of encorafenib by race or ethnicity.

While encorafenib is a relatively potent reversible inhibitor of UGT1A1, no differences in binimetinib exposure have been observed clinically when binimetinib was co-administered with encorafenib.

Encorafenib undergoes minimal renal elimination. No formal clinical study has been conducted to evaluate the effect of renal impairment on the pharmacokinetics of encorafenib. The covariate analysis showed no clear trend evaluating the effect of renal impairment on the encorafenib CL/F in subjects with mild and moderate renal impairment compared with subjects with normal renal function. No relationship between renal function and V/F was found in the population PK analysis. A small decrease in CL/F (≤5%) was predicted for patients with mild and moderate renal impairment, which is unlikely to be clinically relevant. The pharmacokinetics of encorafenib have not been studied in patients with severe renal impairment. A warning has been included in section 4.4 of the SmPC if administering to severe renal impaired patients. No dose adjustment is required for patients with mild or moderate renal impairment based on a population pharmacokinetics (PK) analysis. There are no clinical data with encorafenib in patients with severe renal impairment. Therefore, the potential need for dose adjustment cannot be determined. Encorafenib should be used with caution in patients with severe renal impairment (see SmPC sections 4.2, 4.4 and 5.2).

Results from a dedicated clinical study indicate a 25% higher total encorafenib exposures in patients with mild hepatic impairment (Child-Pugh Class A) compared with subjects with normal liver function. This translates into a 55% increase of the unbound encorafenib exposure. Therefore, a reduced dose of encorafenib 300 mg once daily in patients with mild hepatic impairment (Child Pugh Class A) is recommended in that population (SmPC section 4.2 and 4.4). The pharmacokinetics of encorafenib has not been evaluated clinically in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. As encorafenib is primarily metabolised and eliminated via the liver, based on PBPK modelling, patients with moderate to severe hepatic impairment may have greater increases in exposure than patients with mild hepatic impairment. No dosing recommendation can be made in patients with moderate (Child Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment (see sections 4.2 and 4.4). A warning has been included in section 4.4 of the SmPC for patients with hepatic impairment, where no dosing recommendation can be made in patients with moderate (Child Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment and therefore,.encorafenib is not recommended in patients with moderate or severe hepatic impairment. Closer monitoring of encorafenib related toxicities in patients with mild hepatic impairment is recommended, including clinical examination and liver function tests, with assessment of ECGs as clinically appropriate during treatment.

Encorafenib and binimetinib combination administration can increase QTc interval at the doses used clinically. QT Prolongation has been observed in patients treated with BRAF-inhibitors. A thorough QT study to evaluate the QT prolongation potential of encorafenib has not been conducted.

Overall, results suggest that single agent encorafenib has the potential to cause mild increases in heart rate. Across pooled combination studies of encorafenib and binimetinib at the recommended doses and a single-agent encorafenib study, results suggest that encorafenib has the potential to result in small increases in QTc interval (see section 5.1).

There are insufficient data to exclude a clinically significant exposure dependent QT prolongation.

Due to the potential risk for QT prolongation, it is recommended that serum electrolytes abnormalities, including magnesium and potassium, are corrected and risk factors for QT prolongation controlled (e.g. congestive heart failure, bradyarrhythmias) before treatment initiation and during treatment.

It is recommended that an electrocardiogram (ECG) is assessed before initiation of encorafenib, one month after initiation, and then at approximately 3-month intervals or more frequently as clinically indicated, while on treatment. The occurrence of QTc prolongation can be managed with dose reduction, interruption or discontinuation with correction of abnormal electrolytes and control of risk factors (see section 4.2).

PFS was shorter in patients with higher encorafenib exposure in the Combo 450 arm only. As a confounding factor, baseline LDH was higher in patients with AUCss above the median and PFS was shorter in patients with higher LDH. In the high LDH group in Part 1 of the study only patients with high encorafenib exposure in Combo 450 did worse. There was no such finding with Combo 300 in Part 2. The following is concluded from the updated exposure-response analyses. Nevertheless, addition of binimetinib has a positive effect on the efficacy of encorafenib so combination treatment.

Graphs of the probability of PFS according to encorafenib exposure (AUCss) and ORR and PFS by encorafenib Cmin were provided for Combo 450, Combo 300, Enco 300 Part 1 and Enco 300 Part 2. There was no clear relationship between Cminss of encorafenib and PFS or ORR in Part 1 or Part 2 of the COLOMBUS study for single agent encorafenib or in combination with binimetinib. It was not possible to establish a target Cmin,ss or Ctrough for encorafenib in order to guide dosing. No consistent relationship was observed between AUCss and PFS. The only trend (although not statistically significant) was a decrease in PFS with increased encorafenib AUCss with Combo450 in Part 1. This could have arisen by chance, due to higher baseline LDH levels or be the result of interaction with an unidentified covariate/ confounding factor. Patients with higher baseline LDH levels still had a positive treatment effect with Combo450 compared to vemurafenib in terms of PFS; however, this was not statistically significant with the confidence interval crossing 1 [PFS Combo 450 vs. vemurafenib: high LDH HR 0.73 (95% CI 0.47, 1.14); low LDH HR 0.47 (95% CI 0.33, 0.67)].

2.4.5. Conclusions on clinical pharmacology

The data submitted by the applicant are considered sufficient to adequatey characterise the pharmacokinetic and pharmacodynamic aspects of encorafenib. However, drug interaction will be investigated in a DDI cocktail study aimed to evaluate the DDI of encorafenib and binimetinib as perpetrator on relevant metabolic pathways and transporters. A reduced dose of encorafenib is recommended in patients with mild hepatic impairment while the administration is not recommended in patients with moderate and severe hepatic impairment. This information has been adequately reflected in the SmPC in section 4.2, 4.4 and 5.2. Furthermore, biomarker and genomic analyses would be helpful in supporting pharmacodynamic aspects of the combination therapy.

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 expects 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)

There were 2 early phase studies in patients with V600 mutant tumours (melanoma and colorectal cancer) to provide information on encorafenib dosing.

Phase 1 **Study CLGX818X2101** assessed single agent encorafenib at doses up to 700mg QD. The MTD was determined to be 450mg QD but, due to the number of patients who required dose reduction without experiencing a dose limiting toxicity, encorafenib 300mg QD was declared to be the RP2D. BID dosing was explored briefly but stopped due to poor tolerability.

Table 24: Summary of best overall response by patient and treatment group (FAS, dose escalation phase)

	50 mg qd (N=4) n (%)	100 mg qd (N=10) n (%)	150 mg qd (N=6) n (%)	75 mg bid (N=3) n (%)	200 mg qd (N=4) n (%)	100 mg bid (N=5) n (%)	300 mg qd (N=5) n (%)	150 mg bid (N=4) n (%)	450 mg qd (N=6) n (%)	550 mg qd (N=5) n (%)	700 mg qd (N=2) n (%)	All Mel Nai (N=25) n (%)	All Mel Pre (N=29) n (%)	Encor-afenib All patients (N=54) n (%)
Best overall response														
Complete Response (CR)	1 (25.0)	0	0	0	1 (25.0)	0	0	1 (25.0)	0	0	0	2 (8.0)	1 (3.4)	3 (5.6)
Partial Response (PR)	2 (50.0)	1 (10.0)	3 (50.0)	1 (33.3)	1 (25.0)	2 (40.0)	0	2 (50.0)	2 (33.3)	1 (20.0)	0	13 (52.0)	2 (6.9)	15 (27.8)
Unconfirmed CR	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Stable Disease	0	5 (50.0)	1 (16.7)	2 (66.7)	0	1 (20.0)	2 (40.0)	0	1 (16.7)	2 (40.0)	1 (50.0)	5 (20.0)	10 (34.5)	15 (27.8)
Unconfirmed CR/PR	0	0	0	1 (33.3)	0	0	0	0	0	0	0	1 (4.0)	0	1 (1.9)
Progressive Disease	1 (25.0)	2 (20.0)	2 (33.3)	0	2 (50.0)	1 (20.0)	2 (40.0)	1 (25.0)	2 (33.3)	1 (20.0)	0	0	14 (48.3)	14 (25.9)
Unconfirmed CR/PR	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Unknown	0	2 (20.0)	0	0	0	1 (20.0)	1 (20.0)	0	1 (16.7)	1 (20.0)	1 (50.0)	5 (20.0)	2 (6.9)	7 (13.0)
Unconfirmed CR/PR	0	1 (10.0)	0	0	0	0	0	0	0	0	0	1 (4.0)	0	1 (1.9)
Overall response rate (ORR) (CR or PR)	3 (75.0)	1 (10.0)	3 (50.0)	1 (33.3)	2 (50.0)	2 (40.0)	0	3 (75.0)	2 (33.3)	1 (20.0)	0	15 (60.0)	3 (10.3)	18 (33.3)
95% Confidence interval	(19.4, 99.4)	(0.3, 44.5)	(11.8, 88.2)	(0.8, 90.6)	(6.8, 93.2)	(5.3, 85.3)	(0.0, 52.2)	(19.4, 99.4)	(4.3, 77.7)	(0.5, 71.6)	(0.0, 84.2)	(38.7, 78.9)	(2.2, 27.4)	(21.1, 47.5)
Disease control rate (DCR) (CR or PR or SD)	3 (75.0)	6 (60.0)	4 (66.7)	3 (100)	2 (50.0)	3 (60.0)	2 (40.0)	3 (75.0)	3 (50.0)	3 (60.0)	1 (50.0)	20 (80.0)	13 (44.8)	33 (61.1)
95% Confidence interval	(19.4, 99.4)	(26.2, 87.8)	(22.3, 95.7)	(29.2, 100.0)	(6.8, 93.2)	(14.7, 94.7)	(5.3, 85.3)	(19.4, 99.4)	(11.8, 88.2)	(14.7, 94.7)	(1.3, 98.7)	(59.3, 93.2)	(26.4, 64.3)	(46.9, 74.1)

FAS = Full Analysis Set; Mel = melanoma; nai = naive; pre = pretreated.
Best overall response is based on Investigator's assessment of disease status using RECIST 1.0.
CR and PR are confirmed by repeat assessments performed not less than 4 weeks after the criteria for response is first met.
The 95% Confidence Interval (CI) is calculated using the exact method.
Source: Table 14.2-1.1.1.

Encorafenib monotherapy showed clinical activity at the lowest dose of 50mg QD with wide 95% Cis [ORR= 75% (95%-CI: 19.4; 99.4)].

Phase 1b/ 2 **Study CMEK162X2110** tested encorafenib at doses up to 800mg QD with binimetinib 45mg BID (the RP2D). The MTD was not reached and 2 RP2Ds of encorafenib were declared (450mg & 600mg QD). Patients on 600mg encorafenib plus binimetinib experienced increased serum creatinine so all patients were started on or switched to encorafenib 450mg QD.

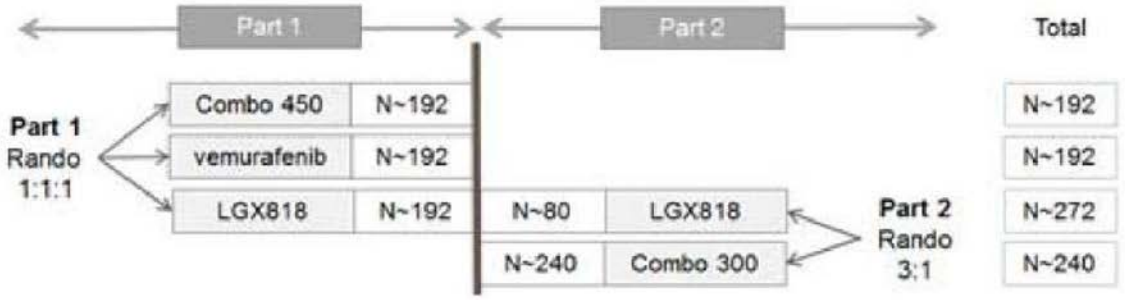
The Phase 3 doses were based on maximum tolerability with the hypothesis that higher doses might prevent the emergence of resistance or prolong the duration of tumour response.

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 ≤ 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 25: 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.

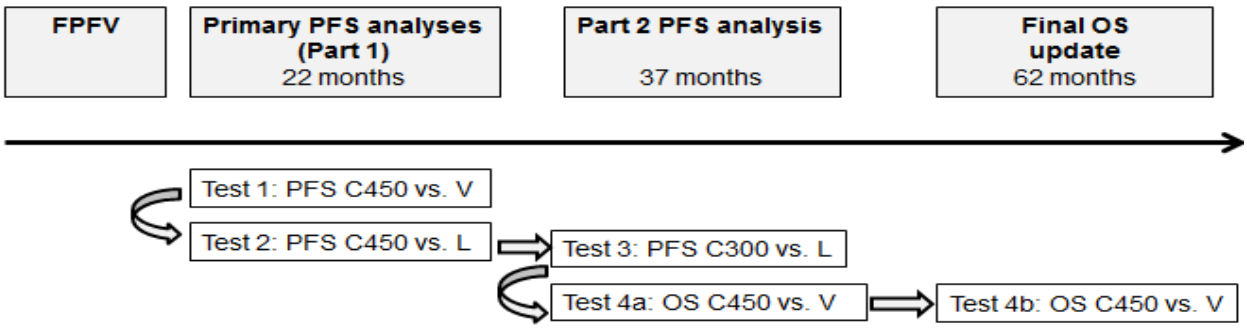


Figure 13: Timing of Testing of Primary and Key Secondary Endpoints (hierarchical testing sequence)

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.

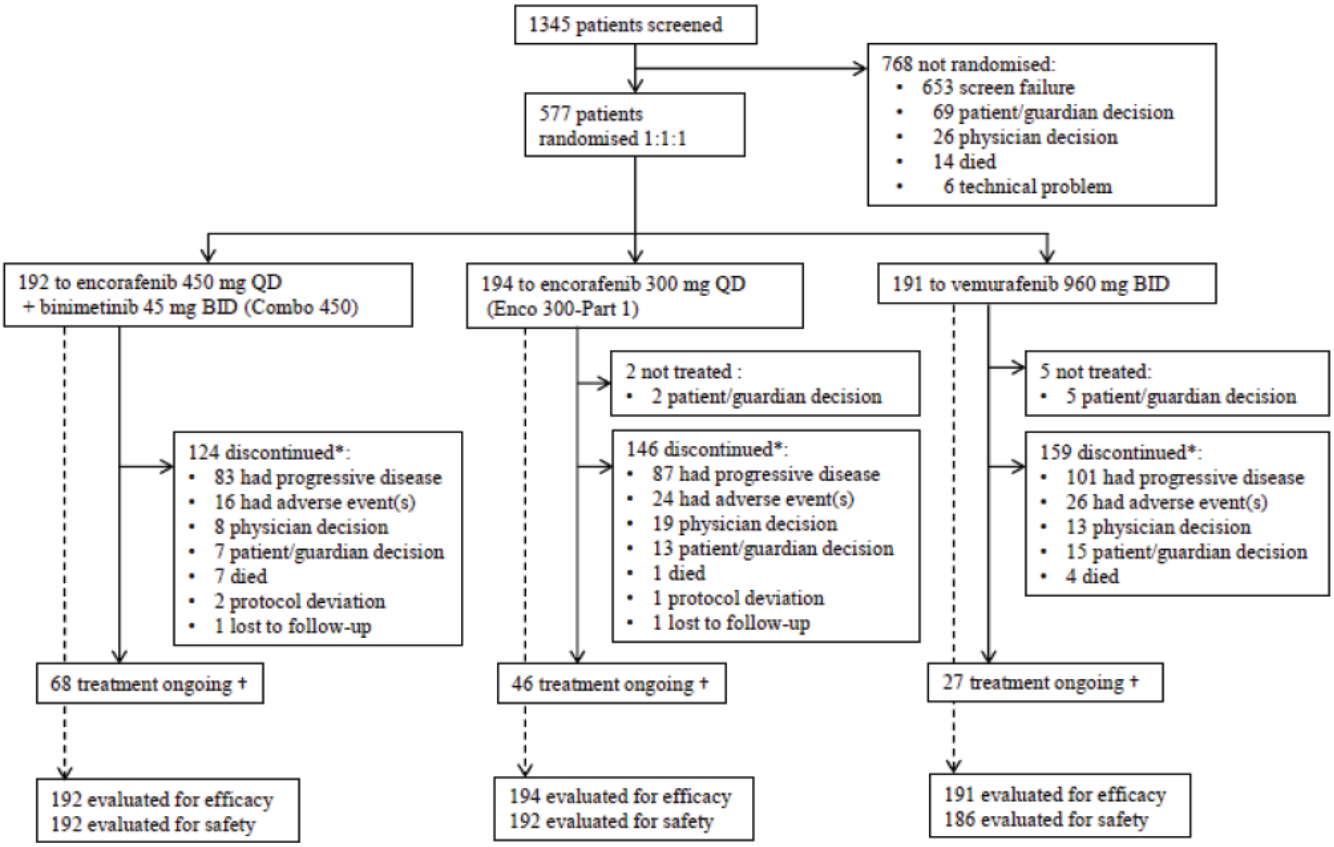
Health-related QoL data were collected via PROs. The FACT-M, EQ-5D-5L and EORTC QLQ-C30 patient questionnaires were used in this study. Health-related QoL data were analyzed using the FAS. The FACT-M melanoma subscale, index score of EQ-5D-5L and the global health status/QoL score of the EORTC QLQ-C30 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 26: 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 27: 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 28: 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 29: 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 30: 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 31: 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 32: 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 33: 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.

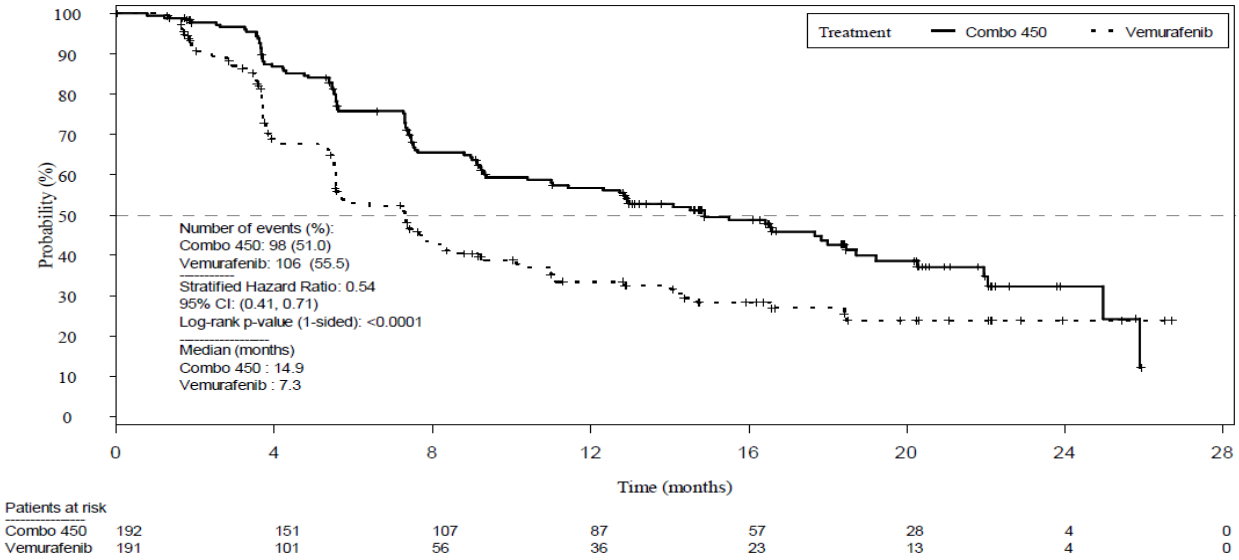


Figure 14: Kaplan-Meier Estimate of PFS Based on BIRC – Combo 450 vs. Vemurafenib (FAS, Part1)

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 34: 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 35: 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.

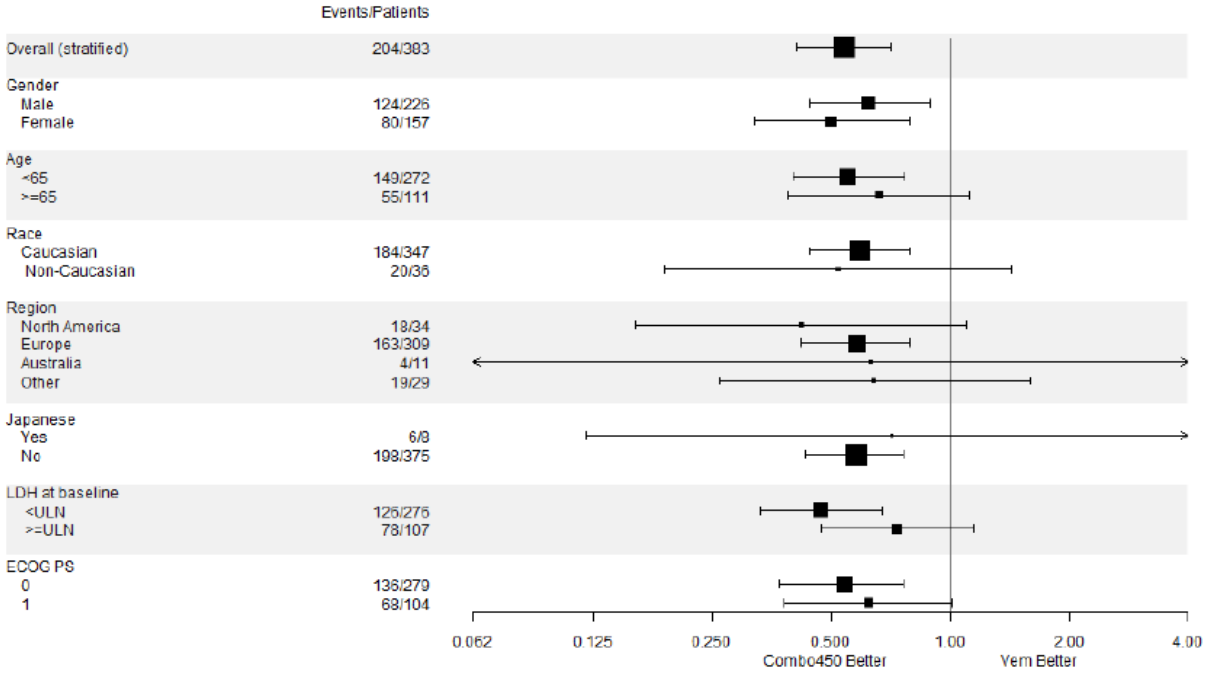
The effect of potential prognostic factors was investigated using a multivariate Cox regression model stratified AJCC stage and ECOG PS.

Table 36: 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.



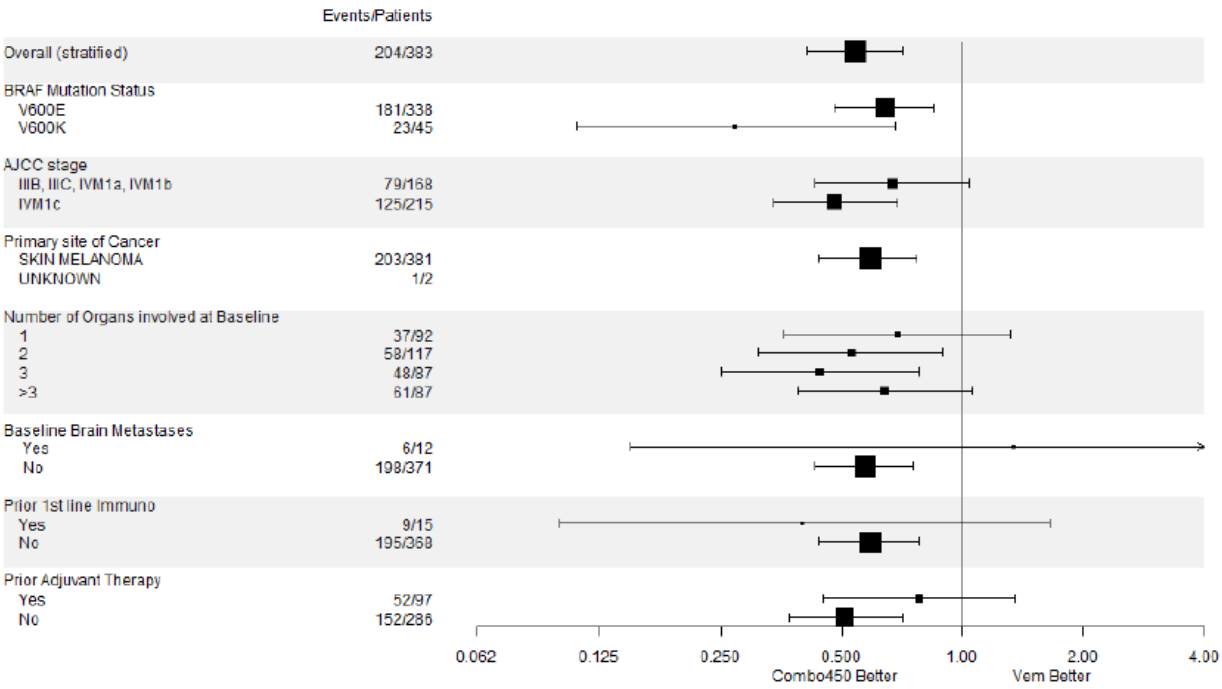


Figure 15: Forest Plot of PFS by BIRC – Combo 450 vs. Vemurafenib (Full Analysis Set, Part 1)

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).

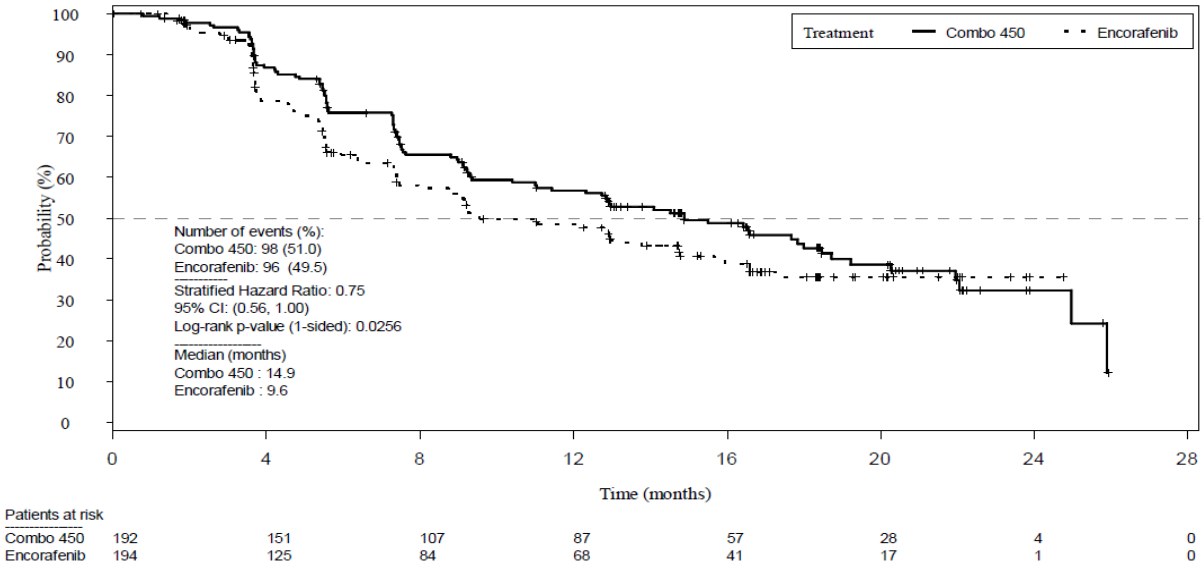


Figure 16: Kaplan-Meier Estimate of PFS Based on BIRC – Combo 450 vs. Encorafenib (FAS, Part 1)

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 37: 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 38: 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 39: 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 40: 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.

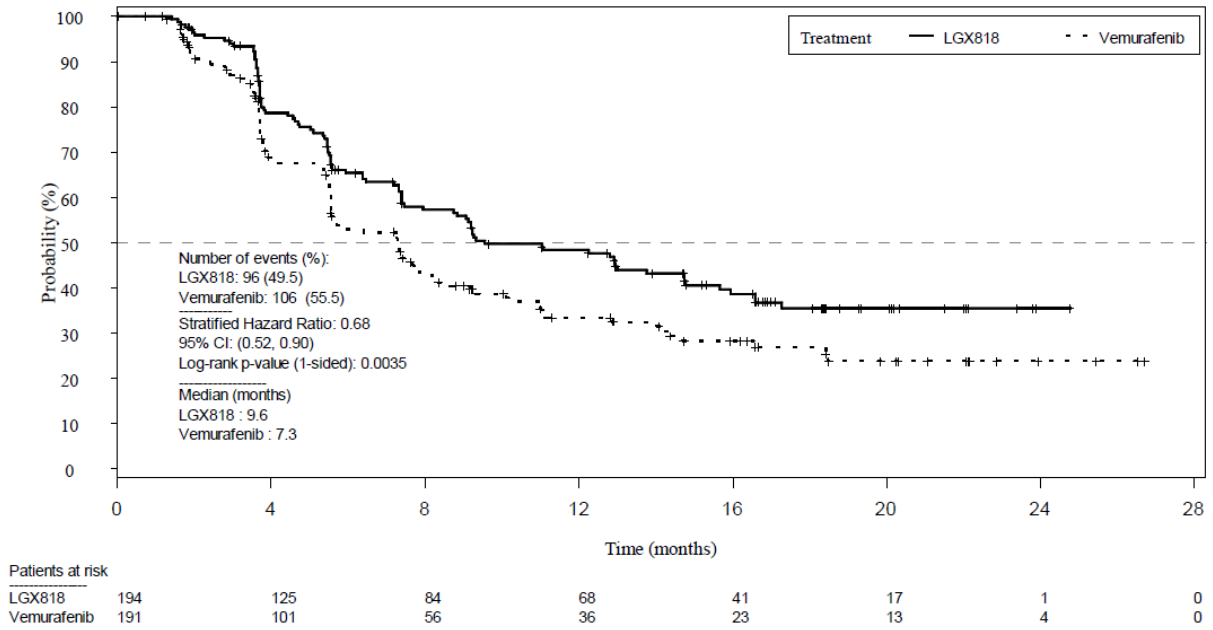


Figure 17: Kaplan-Meier Estimate of PFS Based on BIRC Assessment –Encorafenib vs. Vemurafenib (FAS, Part 1)

Objective Response Rate and Disease Control Rate

Table 41: 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.

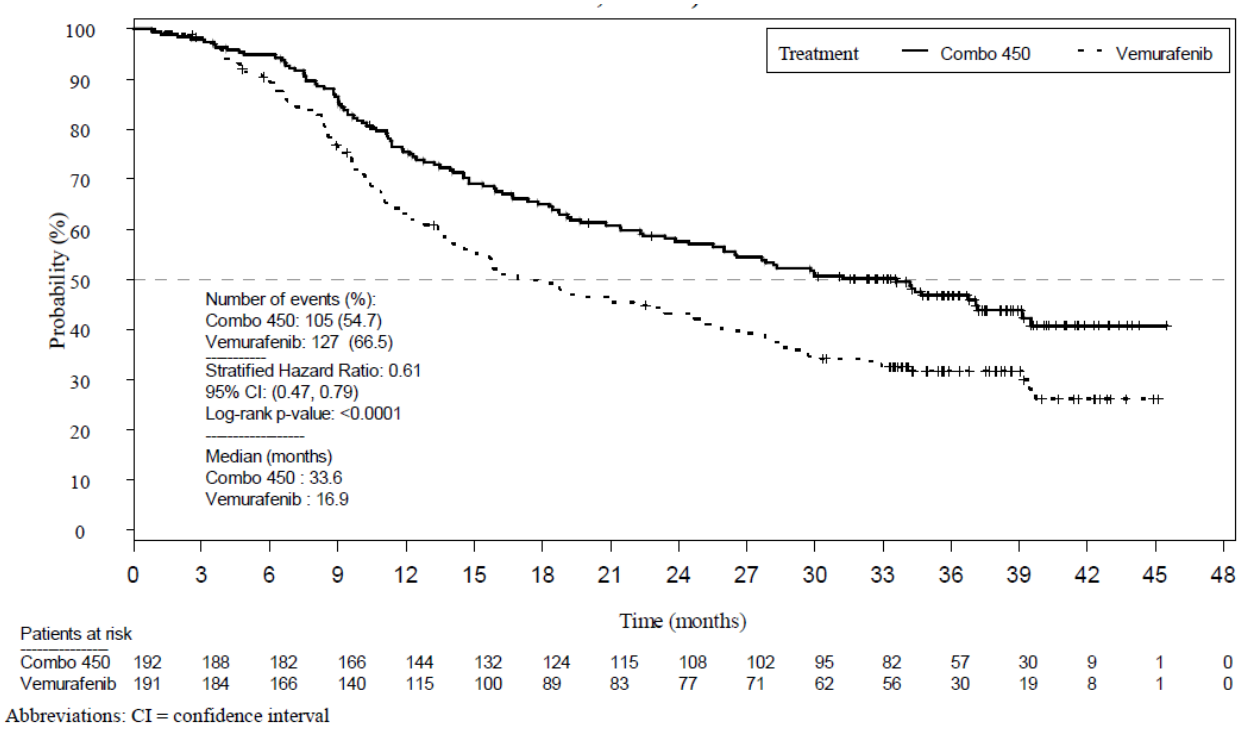


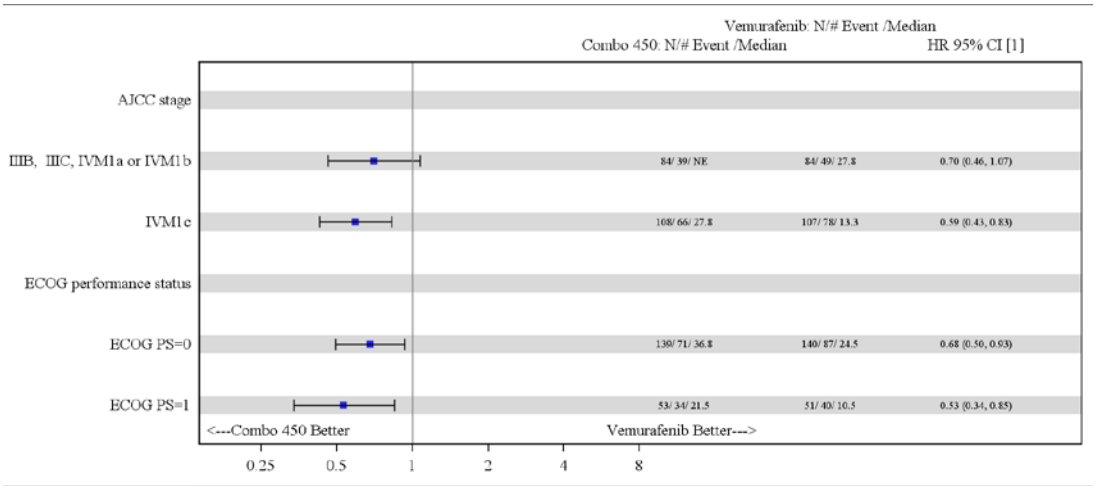
Figure 18: Kaplan-Meier Plot of Overall Survival, Combo 450 vs. Vemurafenib (Full Analysis Set, Part 1)

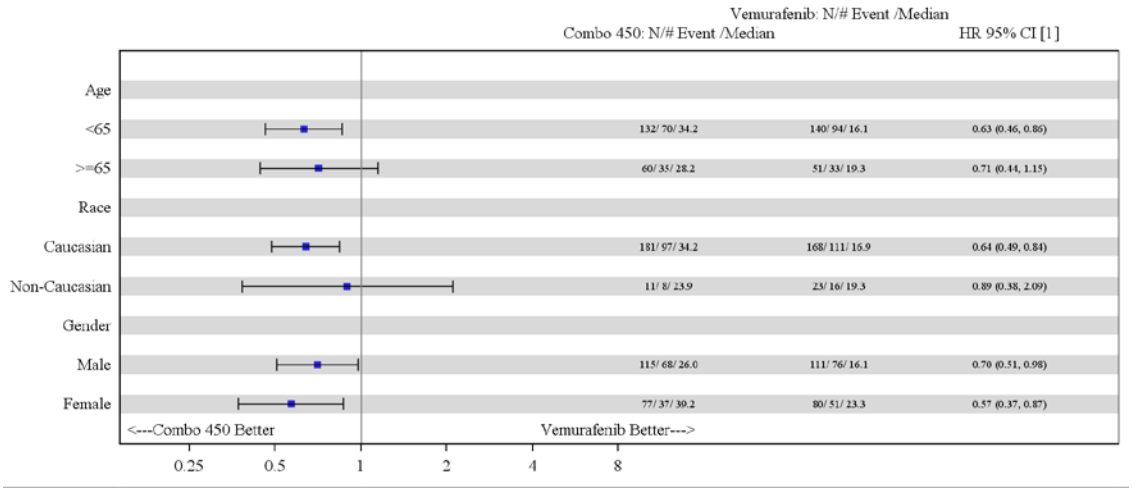
An estimated 39% reduction in the risk of death was observed for patients treated with Combo 450 compared to those treated with vemurafenib (HR 0.61, 95% CI 0.47, 0.79), with median OS values of 33.6 months (95% CI 24.4, 39.2) and 16.9 months (95% CI 14.0, 24.5), respectively.

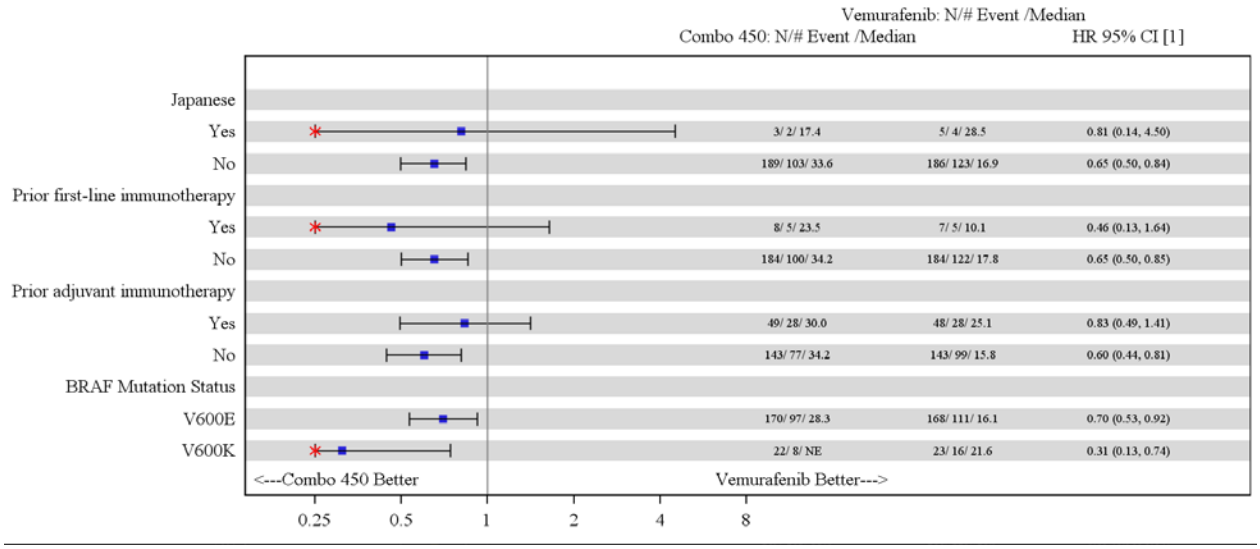
Estimates of OS at 12 months and 24 months were 75.5% (95% CI 68.8, 81.0) and 57.6% (95% CI 50.3, 64.3) for Combo 450 compared to 63.1% (95% CI 55.7, 69.6) and 43.2% (95% CI 35.9, 50.2) for vemurafenib.

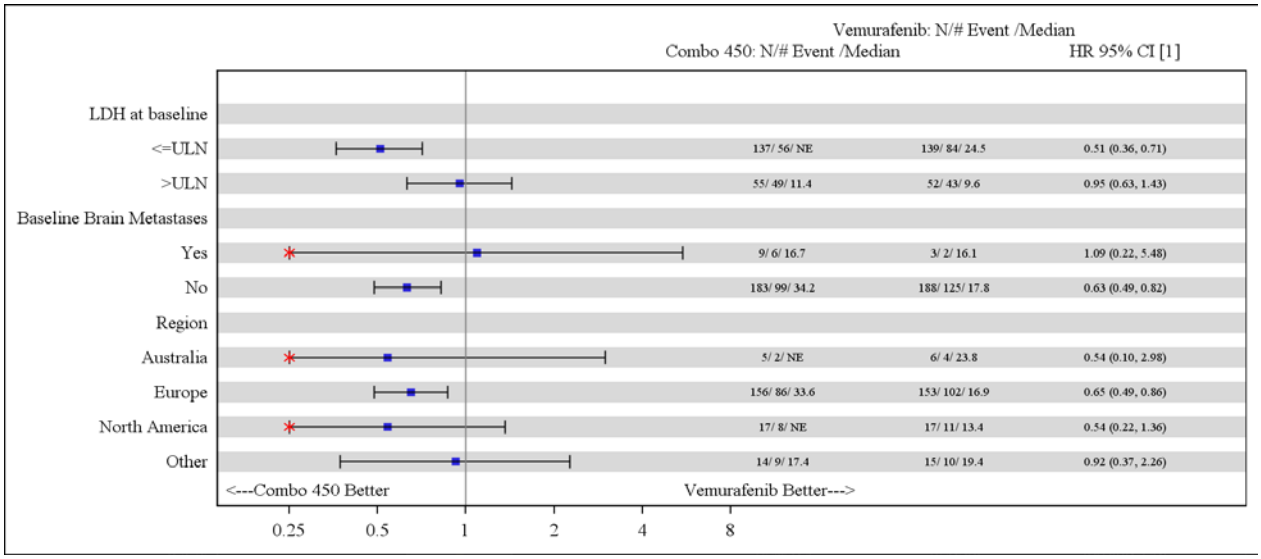
The results of sensitivity analyses are consistent with those of the interim OS analysis and lead to similar conclusions about treatment effect.

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.






Vemurafenib: N/# Event /Median
Combo 450: N/# Event /Median
HR 95% CI [1]
Japanese
Yes
3/ 2/ 17.4
5/ 4/ 28.5
0.81 (0.14, 4.50)
No
189/ 103/ 33.6
186/ 123/ 16.9
0.65 (0.50, 0.84)
Prior first-line immunotherapy
Yes
8/ 5/ 23.5
7/ 5/ 10.1
0.46 (0.13, 1.64)
No
184/ 100/ 34.2
184/ 122/ 17.8
0.65 (0.50, 0.85)
Prior adjuvant immunotherapy
Yes
49/ 28/ 30.0
48/ 28/ 25.1
0.83 (0.49, 1.41)
No
143/ 77/ 34.2
143/ 99/ 15.8
0.60 (0.44, 0.81)
BRAF Mutation Status
V600E
170/ 97/ 28.3
168/ 111/ 16.1
0.70 (0.53, 0.92)
V600K
22/ 8/ NE
23/ 16/ 21.6
0.31 (0.13, 0.74)
<---Combo 450 Better
Vemurafenib Better--->
0.25
0.5
1
2
4
8


Vemurafenib: N/# Event /Median
Combo 450: N/# Event /Median
HR 95% CI [1]
LDH at baseline
<=ULN
137/ 56/ NE
139/ 84/ 24.5
0.51 (0.36, 0.71)
>ULN
55/ 49/ 11.4
52/ 43/ 9.6
0.95 (0.63, 1.43)
Baseline Brain Metastases
Yes
9/ 6/ 16.7
3/ 2/ 16.1
1.09 (0.22, 5.48)
No
183/ 99/ 34.2
188/ 125/ 17.8
0.63 (0.49, 0.82)
Region
Australia
5/ 2/ NE
6/ 4/ 23.8
0.54 (0.10, 2.98)
Europe
156/ 86/ 33.6
153/ 102/ 16.9
0.65 (0.49, 0.86)
North America
17/ 8/ NE
17/ 11/ 13.4
0.54 (0.22, 1.36)
Other
14/ 9/ 17.4
15/ 10/ 19.4
0.92 (0.37, 2.26)
<---Combo 450 Better
Vemurafenib Better--->
0.25
0.5
1
2
4
8

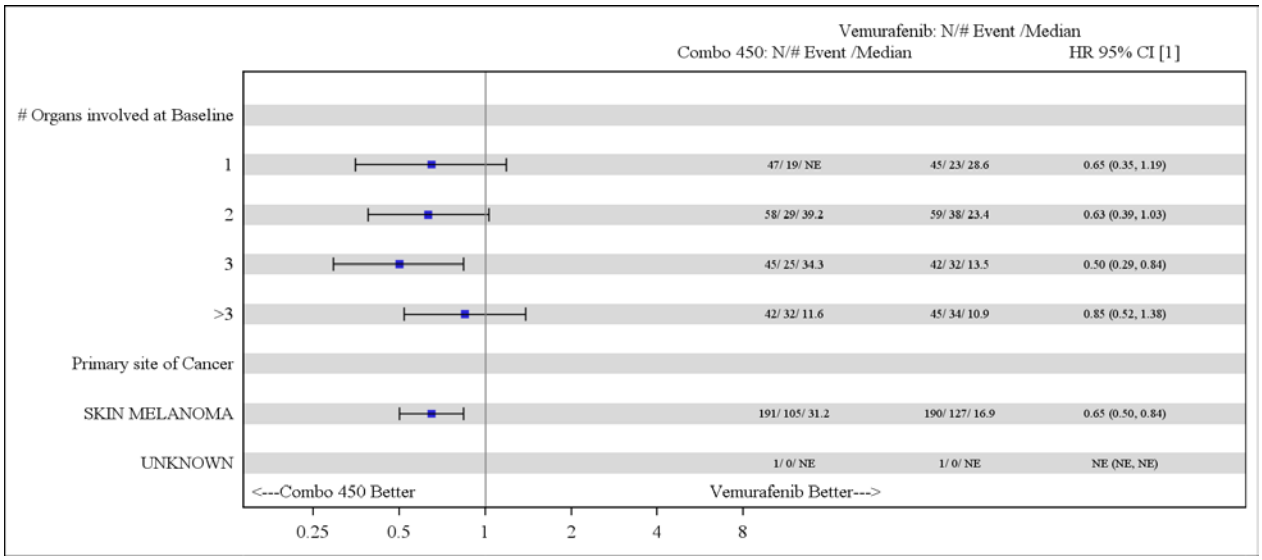
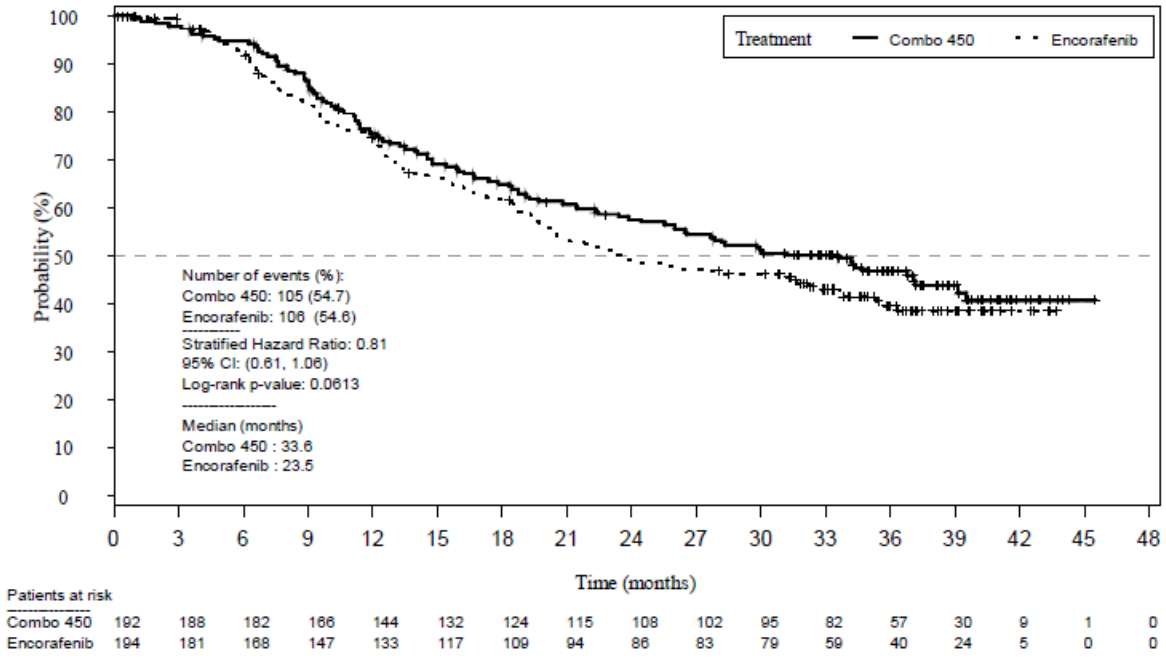


Figure 19: Forest Plot of Hazard Ratio with 95% Confidence Interval for Overall Survival from Subgroup Analysis Encorafenib 450mg+Binimetinib versus Vemurafenib (Full Analysis Set, Part 1)

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 20: 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.

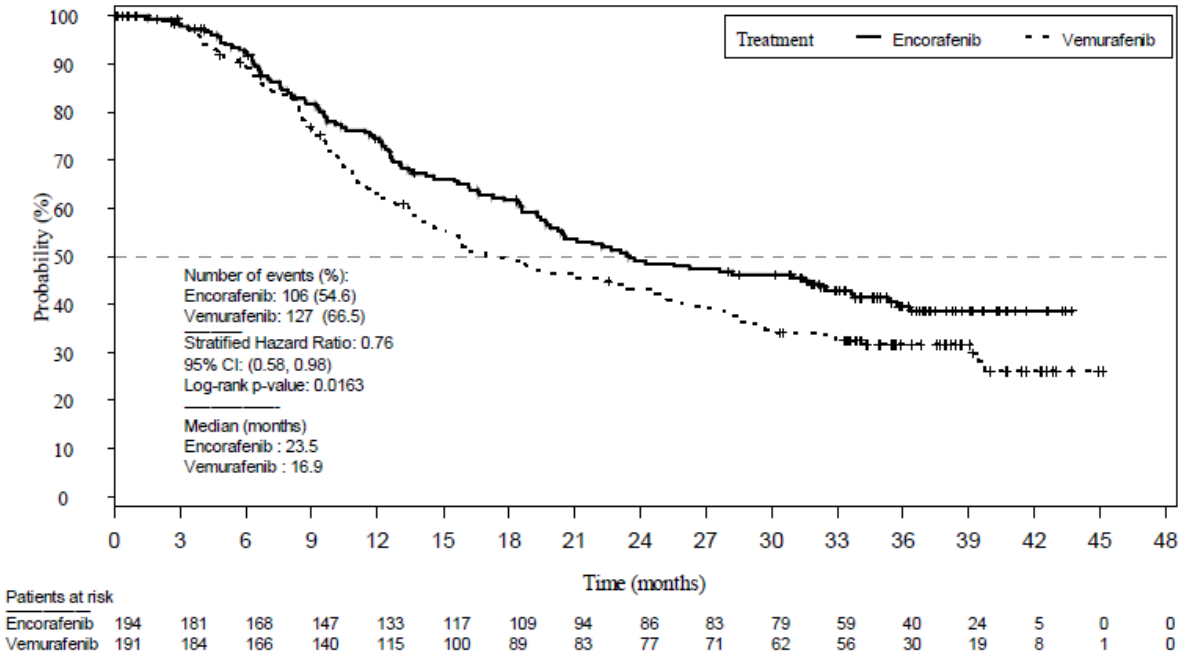


Figure 21: Kaplan-Meier Plot of Overall Survival, Encorafenib vs. Vemurafenib (Full Analysis Set, Part 1)

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 42: 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.

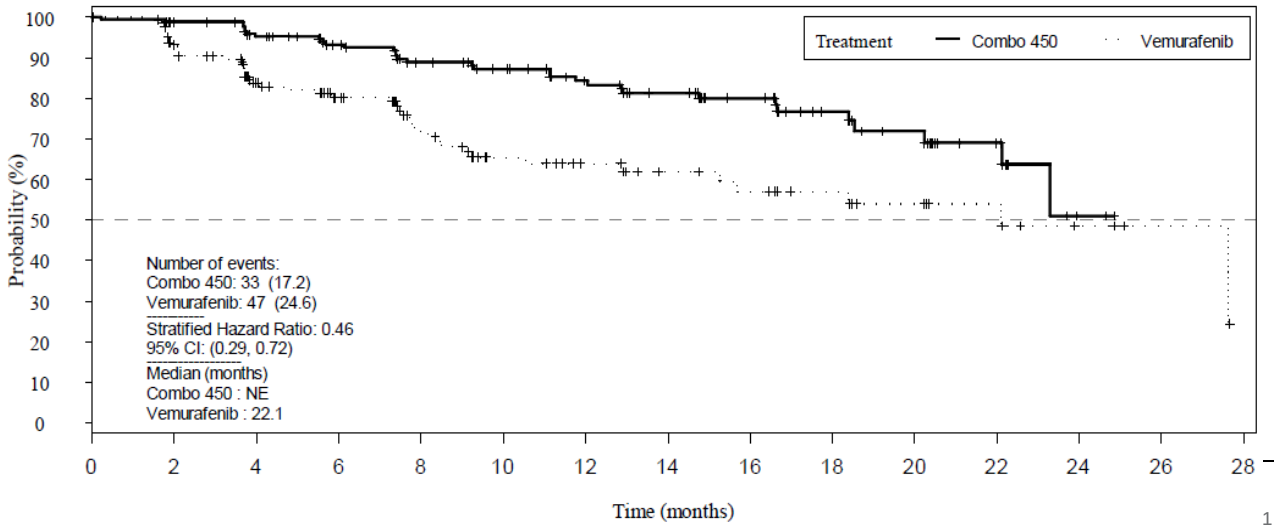


Figure 22: Kaplan-Meier Plot of Time to Definitive 10% Deterioration in FACT-M Global Health Status – Combo 450 vs. Vemurafenib (FAS, Part 1)

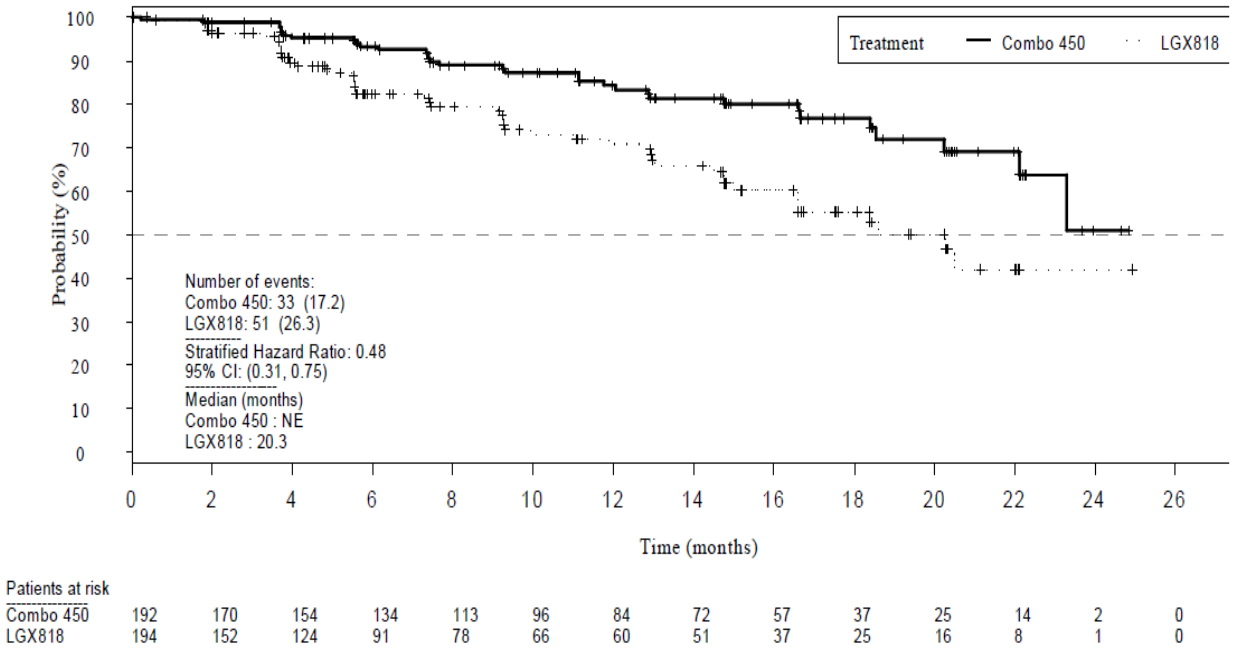


Figure 23: Kaplan-Meier Plot of Time to Definitive 10% Deterioration in FACT-M Global Health Status – Combo 450 vs. Enco 300 (FAS, Part1)

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.

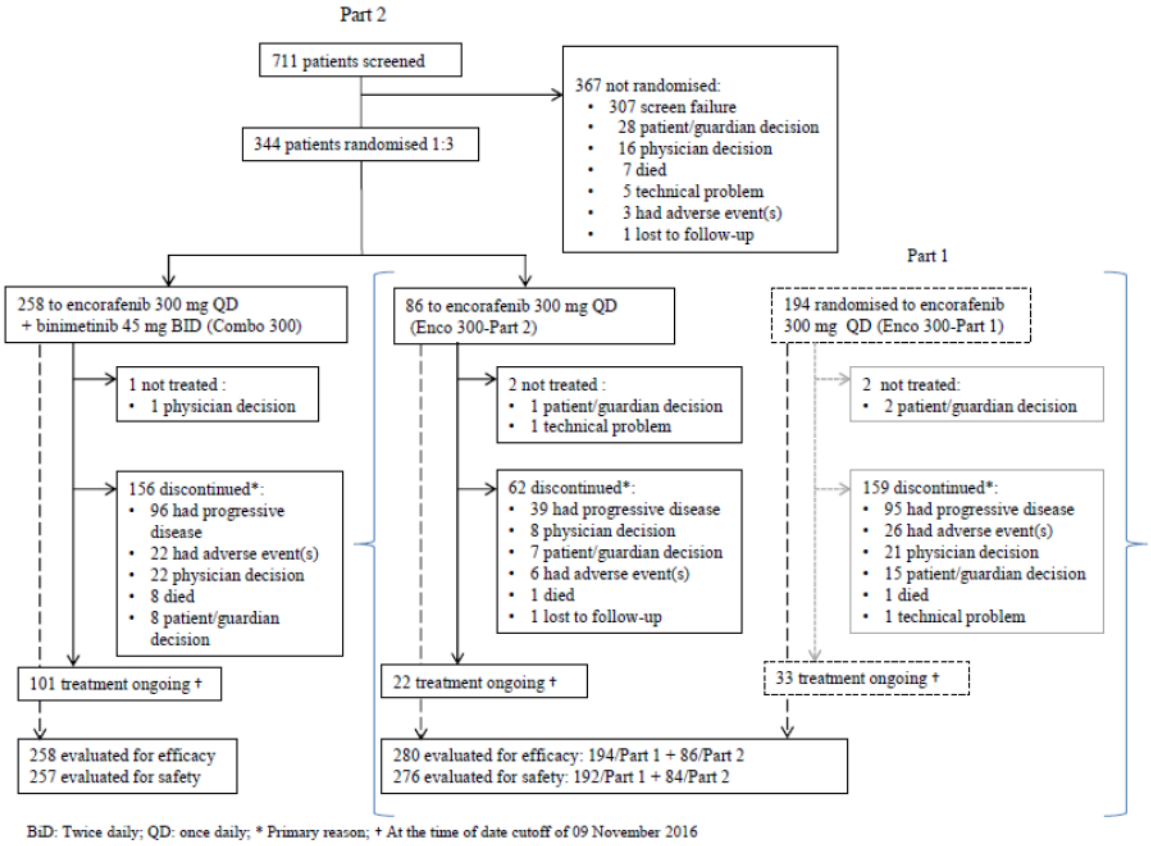


Figure 24: Patient flow chart for Part 2 of study CMEK162B2301

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 43: 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).

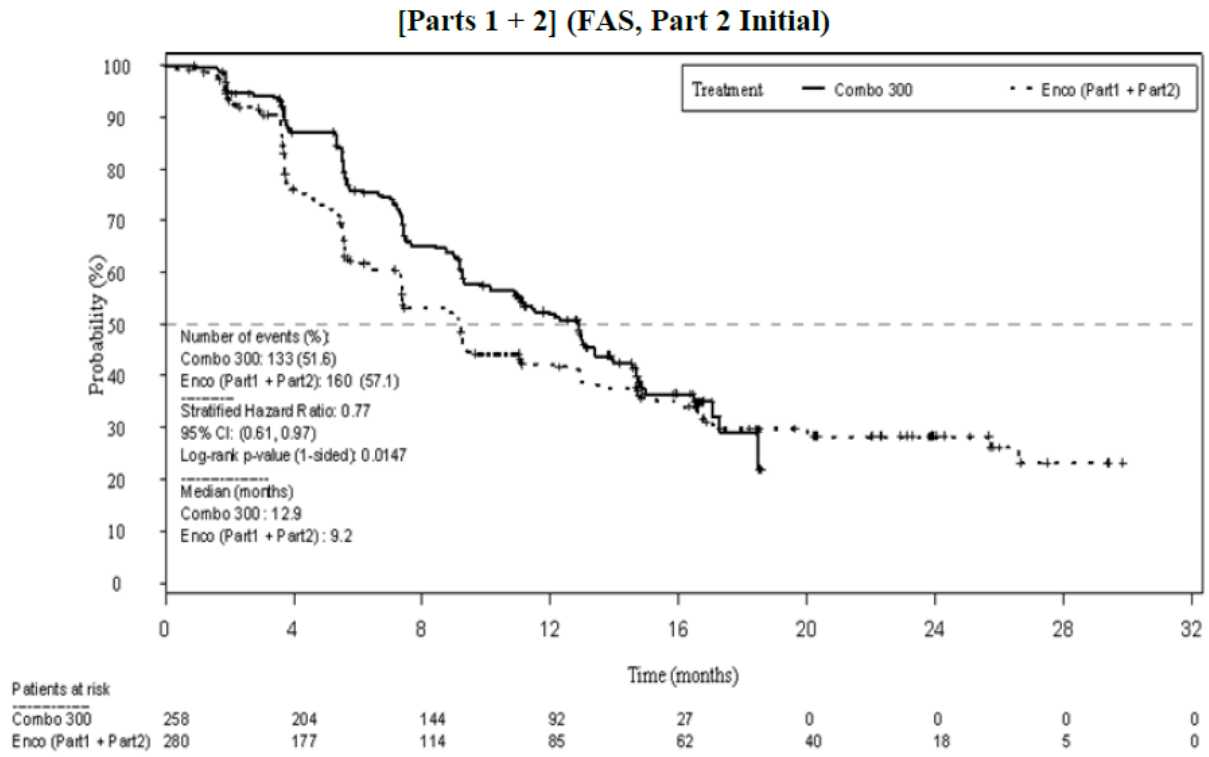


Figure 25: Kaplan-Meier Estimate of PFS Based on BIRC – Combo 300 vs. Enco 300 (Part 1 and 2)

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.

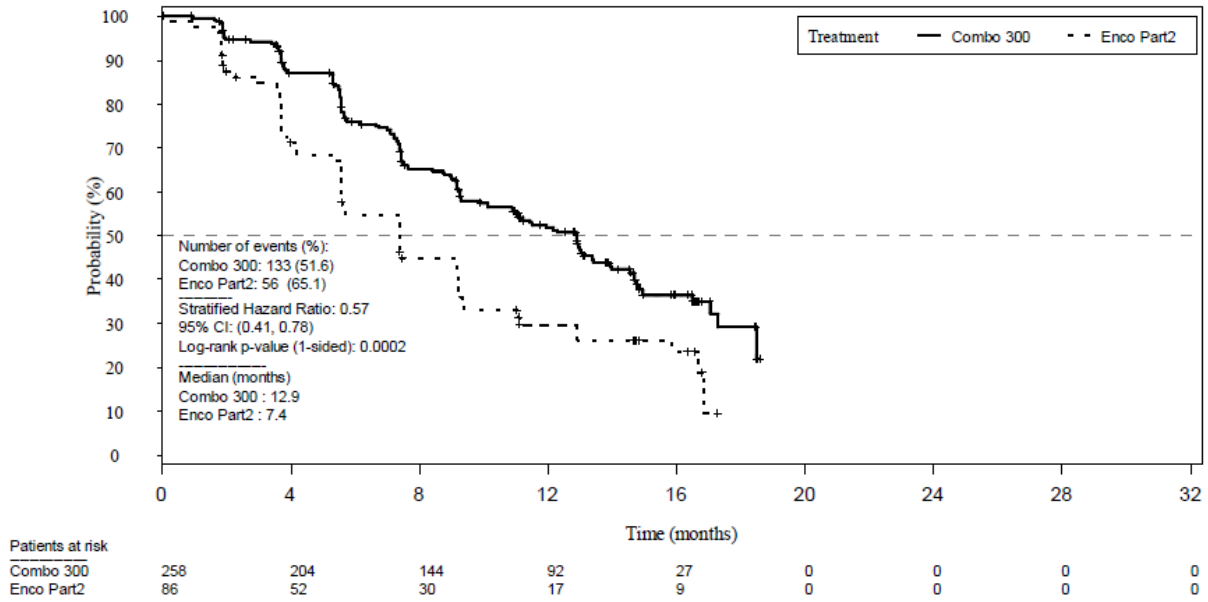


Figure 26: Kaplan-Meier Estimate of PFS Based on BIRC – Combo 300 vs. Enco 300 [Part 2] (FAS, Part 2 Initial)

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.

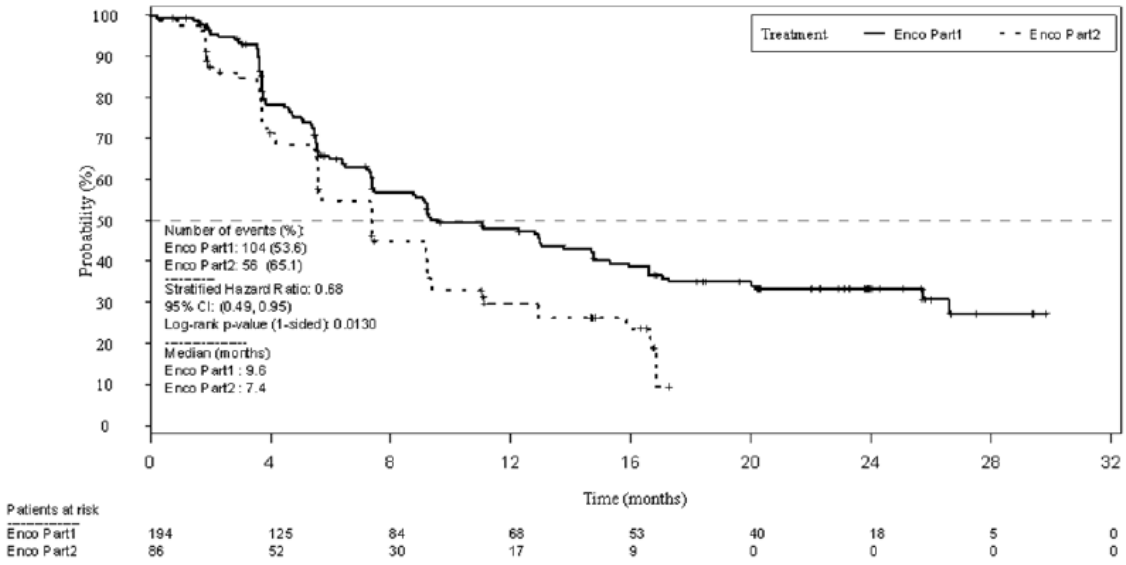


Figure 27: Kaplan-Meier plot of PFS by BIRC - Encorafenib Part 1 vs Encorafenib Part 2 (Full Analysis Set, Part 2 Initial)

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 44: 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).

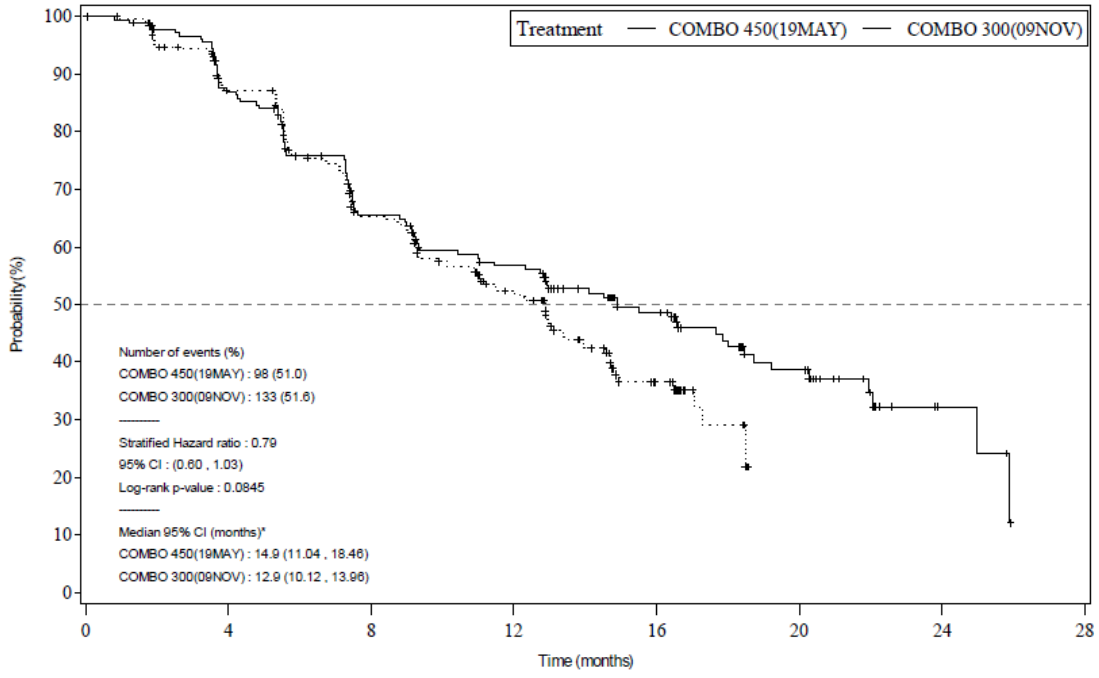
Four PS approaches including stratification (3 and 5 strata), matching, and IPW were then used to estimate the treatment effect on PFS and were adjusted for confounding. The different PS methods (adjusted and non-adjusted) gave HRs ranging from 0.57 to 0.68 and all showed a significant increase in the 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 28: 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 45: 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 46: 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 47: 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 variability	Treatment group	Combo 450	Enco 300	Vemurafenib
	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 48: 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 49: 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 50: 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 51: 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 52: 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)

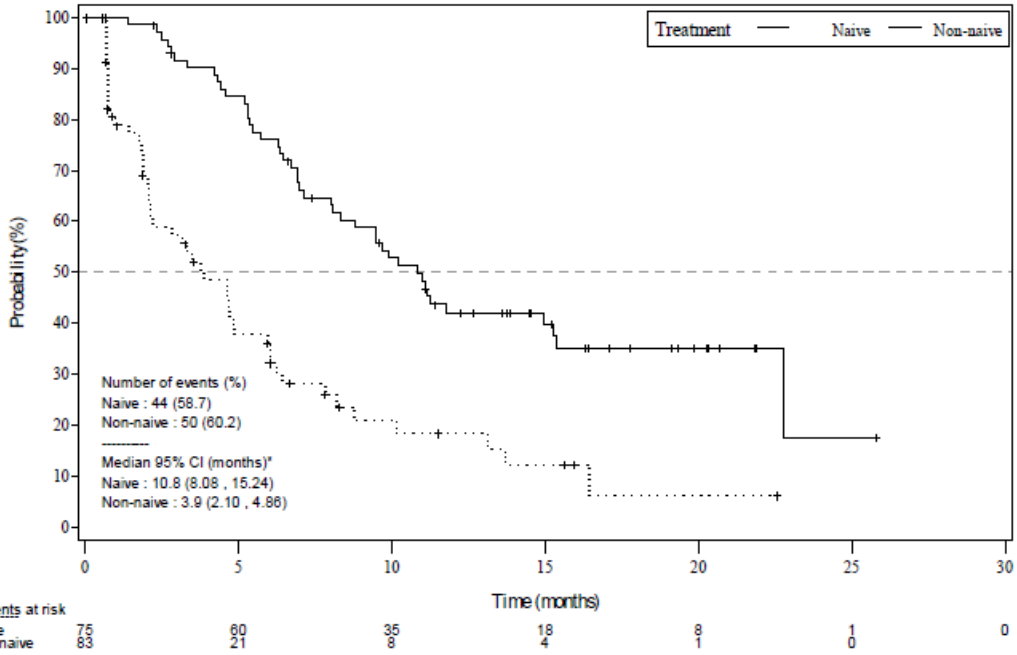
Source: Efficacy Appendix Table Q40BT 3.1
BID: twice daily; BOR: best overall response; Combo 450: binimetinib 45 mg BID in combination with encorafenib 450 mg QD; CR: complete response; DCR: disease control rate; ORR: objective response rate; PD: progressive disease; PR: partial response; QD: once daily; 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 53: 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 54: 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.

2.5.3. 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.

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

BRAF mutation testing

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

Encorafenib in combination with binimetinib in patients who have progressed on a BRAF inhibitor

There are limited data for the use of the combination of encorafenib with binimetinib 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.

Encorafenib in combination with binimetinib in patients with brain metastases

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

Paediatric population

The safety and efficacy of encorafenib have not yet been established in children and adolescents. No data are available.

The European Medicines Agency has deferred the obligation to submit the results of studies with encorafenib in one or more subsets of the paediatric population in melanoma (see section 4.2 for information on paediatric use).

2.5.4. 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

Patient exposure

As of 11 May 2016, a total of 1495 subjects (91 healthy volunteers and 1404 patients with advanced cancer) had been exposed to encorafenib. Safety data from 5 clinical trials in patients with unresectable or metastatic *BRAF* V600 mutant melanoma were presented in overlapping populations.

For combination treatment:

‘Combo 450’: (N=192) treated with 450 mg QD encorafenib plus 45 mg BID binimetinib in Phase 3 study CMEK162B2301 Part 1

‘Combo 450 RP’: ‘restricted’ combination, (N=274) treated with Combo 450 in CMEK162B2301 Part 1 (n=192), CLGX818X2109 Part A (n=75) and CMEK162X2110 previously naïve to BRAF inhibitors (n=7)

‘Combo 450 BP’: ‘broad’ combination, (N=433) treated with encorafenib 300mg-600mg QD (higher/ lower encorafenib doses outside this range were not pooled) and binimetinib 45mg BID in CMEK162B2301 Part 1 (n=192), CLGX818X2109 (n=158) and CMEK162X2110 (n=87). The number of patients treated with encorafenib doses other than 450mg QD vs those who were not BRAF/ MEK inhibitor naïve was not presented.

For encorafenib monotherapy treatment:

‘Enco 300’: (N=192) treated with 300mg QD encorafenib in Study CMEK162B2301 Part 1

‘Enco 300 P’: (N=217), treated with 300mg QD encorafenib in CMEK162B2301 Part 1 (=192) and BRAF inhibitor naïve patients from CLGX818X2102 and CLGX818X2101 (n=25)

These were compared to the vemurafenib 960mg BID arm of the Phase 3 study (N=186).

In the Combo 450 RP population, the median duration of combination binimetinib and encorafenib exposure was 41.9 weeks, with 121 patients (44.2%) exposed to treatment for ≥48 weeks. The median duration of exposure was shorter in the Enco 300 P population (29.7 weeks) with 77 patients (35.5%) exposed to treatment for ≥48 weeks.

A similar median relative dose intensity (RDI) was reported for each component (binimetinib 99.6%, encorafenib 100%) of the Combo 450 RP population with an RDI of 100% for 44.5% and 50% of patients for binimetinib and encorafenib, respectively. The median RDI of encorafenib was lower in the Enco 300 P monotherapy population (87.5%) and the proportion with an RDI of 100% was only 28.1%. Exposure in most subgroups in the Combo 450 RP population was close to the median. Median exposure was lower in patients with baseline liver metastases (N=97), Asian patients and patients with moderate renal impairment but still >32 -36 weeks and the last 2 groups involved small patient numbers (n=6 and 4, respectively). Duration of treatment in the single patient ≥85 years was only 14 weeks.

A 4-month safety update was provided in response to the Day 120 list of questions, focussing on pooled data from the same studies as presented in the initial MAA. The data cut-off dates and number of patients in each study included in the pooled analyses are presented below. The 4-month safety update provides an additional 750 patient-months of exposure in the Combo 450 RP population and 219 patient-months in the Enco 300 P population.

Table 55: Clinical Studies Included in Pooled Safety Summaries (Initial MAA and 4-Month Safety Update)

Study	Initial MAA		4-Month Safety Update	
	Cut-off Date	Pts Included in Pooled Summaries	Cut-off Date	Pts Included in Pooled Summaries
Encorafenib + Binimetinib Combination				
CMEK162B2301 Part 1	19 May 2016	192	09 Nov 2016	192
CLGX818X2109	18 Feb 2016	158	30 Dec 2016	158
CMEK162X2110	31 Aug 2015	87	31 Dec 2016	87
Single-agent Encorafenib				
CMEK162B2301 Part 1	19 May 2016	192	09 Nov 2016	192
CLGX818X2101	18 Aug 2014	10	Same as initial MAA[a,b]	
CLGX818X2102	05 May 2015	15	Same as initial MAA[a,b]	

Abbreviations: CSR = clinical study report; MAA =: Marketing Authorisation Application; Pts = patients; SAE = serious adverse event

[a] Same cutoff date as initial MAA due to minimal/no data changes.

[b] Listing of treatment-emergent SAEs occurring between the cut-off dates for the initial MAA to 31 Dec 2016 is provided for Studies CLGX818X2101 and CMEK162A2301. For Studies CLGX818X2102 and CMEK162X2201, no treatment emergent-SAEs occurred during this timeframe (Module 5.3.5.3, SAE Listings).

The median duration of exposure was 11.7 months in patients treated with Combo 450, 7.1 months in patients treated with Enco 300 and 6.2 months in patients treated with vemurafenib. The median duration of exposure to study treatment in the Combo 450 RP population increased by ~9 weeks from 41.9 to 50.6 weeks, with 142 patients (51.8%) exposed to treatment for ≥48 weeks (increase by nearly 8%). In the Enco 300 P population, the median duration of exposure to study treatment (29.7 weeks) and the percentage of patients exposed to treatment for ≥48 weeks (35.5%) were unchanged.

The median relative dose intensity (RDI) for Combo 450 was 100% for encorafenib and 99.6% for binimetinib; the median RDI was 86.2% for Enco 300 and 94.5% for vemurafenib. The median relative dose intensity decreased slightly (< 5.0%) for the Enco 300 P population, (84.98% vs 87.53% in the initial MAA), although the number of patients (n=61, 28.1%) receiving a relative dose intensity of 100% remained unchanged.

In the Combo 450 RP population, the median relative dose intensity of encorafenib and binimetinib was 99.66% and 99.50%, respectively, similar to that reported in the initial MAA. The relative dose intensity in the Combo 450 RP population at the 4-month safety update for encorafenib was 100% in 123 patients (44.9%) and 100% for binimetinib in 109 patients (39.8%).

Adverse events

For Combo 450 P, the incidence of AEs was 98.9% with Grade 3/4 AEs reported in 57.8% patients (Grade 3, 48.2%; Grade 4, 9.9%); the median time to onset of the first Grade 3/4 AE was 2.5 months.

For Enco 300 P, the incidence of AEs was 99.5% with Grade 3/4 AEs observed in 67.3% patients (Grade 3, 58.1%; Grade 4, 9.2%); the median time to onset of the first Grade 3/4 AE was 0.4 months.

For vemurafenib, the incidence of AEs was 98.4%, with Grade 3/4 AEs in 63.4% patients (55.4% Grade 3 AEs and 8.1% Grade 4 AEs); the median time to onset of first Grade 3/4 AEs was 1.3 months.

Table 56: Overall Summary of Adverse Events by Treatment

	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]	15 (6.5)	44 (10.2)	23 (8.4)	17 (8.9)	14 (7.3)	19 (10.2)
AE	216 (99.5)	426 (98.4)	271 (98.9)	189 (98.4)	191 (99.5)	185 (99.5)
Grade 3/4	146 (67.3)	254 (58.7)	159 (58.0)	111 (57.8)	127 (66.1)	118 (63.4)
SAE	69 (31.8)	158 (36.5)	98 (35.8)	66 (34.4)	65 (33.9)	69 (37.1)
Grade 3/4	58 (26.7)	142 (32.8)	87 (31.8)	57 (29.7)	54 (28.1)	60 (32.3)
AE leading to treatment discontinuation	38 (17.5)	45 (10.4)	28 (10.2)	24 (12.5)	27 (14.1)	31 (16.7)
Grade 3/4	29 (13.4)	33 (7.6)	24 (8.8)	22 (11.5)	21 (10.9)	18 (9.7)
AE requiring dose interruption and/or change	152 (70.0)	208 (48.0)	129 (47.1)	92 (47.9)	135 (70.3)	114 (61.3)
Grade 3/4	93 (42.9)	142 (32.8)	88 (32.1)	63 (32.8)	85 (44.3)	71 (38.2)
AE requiring additional therapy [b]	189 (87.1)	364 (84.1)	236 (86.1)	165 (85.9)	181 (94.3)	171 (91.9)
Grade 3/4	107 (49.3)	160 (37.0)	101 (36.9)	67 (34.9)	106 (55.2)	91 (48.9)

[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

Table 57: Overall summary of relevant intra-population differences since initial MAA in the Enco 300P and COMBO 450 RP (Restricted Safety Set)

		Initial MAA		4-month safety update	
		Enco 300mg QD N=217 n (%)	Combo 450mg QD N=274 n (%)	Enco 300mg QD N=217 n (%)	Combo 450mg QD N=274 n (%)
On-treatment deaths [1]		15 (6.9)	**23 (8.4)**	16 (7.4)	**28 (10.2)**
Adverse events (AEs)	All Grades	216 (99.5)	271 (98.9)	216 (99.5)	271 (98.9)
	Grades 3-4	**109 (50.2)**	159 (58.0)	**147 (67.7)**	168 (61.3)
Serious AEs	All Grades	69 (31.8)	**98 (35.8)**	71 (32.7)	**110 (40.1)**
	Grades 3-4	58 (26.7)	87 (31.8)	60 (27.6)	94 (34.3)
AEs leading to discontinuation	All Grades	38 (17.5)	28 (10.2)	39 (18.0)	32 (11.7)
	Grades 3-4	29 (13.4)	24 (8.8)	28 (12.9)	26 (9.5)
AEs requiring dose interruption and/or adjustment	All Grades	152 (70.0)	**130 (47.4)**	154 (71.0)	**143 (52.2)**
	Grades 3-4	93 (42.9)	88 (32.1)	96 (44.2)	94 (34.3)
AEs requiring additional therapy [2]	All Grades	205 (94.5)	236 (86.1)	206 (94.9)	246 (89.8)
	Grades 3-4	120 (55.3)	**101 (36.9)**	120 (55.3)	**110 (40.1)**

QD – once daily; Bold text denotes the relevant intra-population difference since the initial MAA.
Source: ISS Table 2.2.1 and ISS Part1 u Table 2.2.1-u
[1] Deaths occurring >30 days after end of treatment are not included.
[2] Additional therapy includes all non-drug therapy and concomitant medications.

The incidence of patients in the Enco 300P population with at least one dose modification of encorafenib was unchanged [155 of 217 (71.4%)].

In the Combo 450 RP population, the incidence of dose modifications had slightly increased; 147 of 274 (53.6%) required at least 1 dose modification of encorafenib, 164 of 274 (59.9%) required at least 1 dose modification of binimetinib. Modification of encorafenib dose due to an AE occurred in 41.2% of patients, including dose reductions (17.5%) and dose interruptions (38.7%). Modification of binimetinib dose due to an AE occurred in 45.6% of patients, including dose reductions (30.7%) and dose interruptions (40.5%).

The proportion of patients requiring at least one dose modification of encorafenib due to an AE (including dose reductions and interruptions) remained lower in the Combo 450 RP compared to the Enco 300 P population:

- 53.6% vs 71.4% of patients with dose modifications for any reason
- 41.2% vs 65.9% of patients with dose modifications due to AEs.

Table 58: Adverse Events, Regardless of Study Drug Relationship, by System Organ Class by Treatment – Overall and Maximum Grade 3 or 4 (≥20% in any population)

	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)
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)
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)
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)
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)
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)
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)
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)
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)
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)
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)
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)
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)
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
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)

Table 59: Relevant intra -population differences since initial MAA in incidences of AEs and Grade 3/4 AEs whatever relationship to study treatment by Primary SOC (≥ 20% in any population) (Restricted Safety Set)

Parameter	Initial MAA	4-month safety update
Intra-population differences in incidences*		
Combo 450 RP; N=274		
By SOCS – all grades (grade 3-4)		
Overal incidence	98.9% (58.0%)	98.9% (61.3%)
Blood and lymphatic system disorders	23.0% (6.2%)	25.5% (6.6%)
Eye disorders	57.7% (2.2%)	61.7% (2.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	21.9 % (2.2%)	24.5 % (4.4%)
Injury poisoning	13.1% (1.1%)	17.9% (1.5%)
Reproductive system disorder –	9.9% (0.0)	12.4% (0.7%)
Respiratory, thoracic and mediastinal disorders	27.7% (2.6%)	31.4% (3.3%)
Nervous system disorders	26% (9.5%)	31% (11.3%)
By PTs – all grades (grade 3-4)		
Arthralgia	24.8%	27.0%
Blood CK increased	24.8%	27.0%
Asthenia	13.9%	15.7%
Muscle spasms	11.3%	13.5%
Hyperkeratosis	12.4%	13.5%
Dizziness	11.3%	12.4%
Back pain	8.8%	10.9%
Enco 300 P; N=217		
By SOCS – all grades (grade 3-4)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	38.2% (6.6%)	40.5% (6.3%)
Eye disorders	26.7% (0.5%)	30.5% (0.5%)
Metabolism and nutrition disorder	34.6% (8.3%)	31.6% (6.6%)
By PTs	NA	NA

Adjusted for exposure, the rate of AEs was lower in the Combo 450 RP population compared to the Enco 300 P population (142.83 vs 604.83 per 100 patient-months) and compared to vemurafenib (226.32 per 100 patient-months).

When individual AEs were adjusted for duration of exposure, the rate of diarrhoea (4.87 vs 1.46 per 100 pt-mnths) and increased CK (2.66 vs 0.1 per 100 pt-mnths) was higher with combination treatment; the rates of alopecia (1.39 vs. 13.14) , PPE (0.55 vs. 10.45), arthralgia (2.71 vs. 8.4), hyperkeratosis (1.23 vs. 7.13) and rash (12.0 vs. 21.7) were higher with single agent encorafenib (Combo 450 RP vs. Enco 300P).

At the 4 month update no new PTs were reported with an exposure-adjusted incidence rate (EAIR) ≥5 per 100 patient-months in the Combo 450 RP or Enco 300 P populations.

Table 60: Adverse Events, Regardless of Study Drug Relationship, Adjusted for Patient-month Exposure, by Preferred Term and Treatment (Exposure Adjusted Incidence Rate - EAIR ⩾5 in any population)

	Melanoma				Study CMEK162B2301		
Preferred Term	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							
n (%) [1]	427 (100)	216 (99.5)	426 (98.4)	271 (98.9)	189 (98.4)	191 (99.5)	185 (99.5)
Exposure (months) [2]	108.39	35.71	241.64	189.73	160.39	33.87	81.74
EAIR [3]	393.96	604.83	176.29	142.83	117.83	563.88	226.32
Nausea							
n (%) [1]	128 (30.0)	82 (37.8)	178 (41.1)	108 (39.4)	79 (41.1)	74 (38.5)	63 (33.9)
Exposure (months) [2]	1475.09	1396.04	2705.68	2073.2	1569.45	1299.81	1128.94
EAIR [3]	8.68	5.87	6.58	5.21	5.03	5.69	5.58
Diarrhoea							
n (%) [1]	182 (42.6)	27 (12.4)	161 (37.2)	99 (36.1)	70 (36.5)	26 (13.5)	63 (33.9)
Exposure (months) [2]	1142.64	1854.29	2655.34	2034.17	1579.4	1711.41	1076.93
EAIR [3]	15.93	1.46	6.06	4.87	4.43	1.52	5.85
Fatigue							
n (%) [1]	114 (26.7)	60 (27.6)	135 (31.2)	83 (30.3)	55 (28.6)	48 (25.0)	57 (30.6)
Exposure (months) [2]	1439.61	1527.23	3004.88	2308.44	1820.12	1442.86	1130.28
EAIR [3]	7.92	3.93	4.49	3.6	3.02	3.33	5.04
Vomiting							
n (%) [1]	84 (19.7)	58 (26.7)	123 (28.4)	73 (26.6)	57 (29.7)	52 (27.1)	28 (15.1)
Exposure (months) [2]	1588.34	1644.32	3307.1	2454.21	1869.93	1524.34	1385.59
EAIR [3]	5.29	3.53	3.72	2.97	3.05	3.41	2.02
Arthralgia							
n (%) [1]	31 (7.3)	93 (42.9)	100 (23.1)	68 (24.8)	49 (25.5)	84 (43.8)	83 (44.6)
Exposure (months) [2]	1671.33	1107.22	3347.98	2509.96	1914.78	1011.71	828.98
EAIR [3]	1.85	8.4	2.99	2.71	2.56	8.3	10.01
Blood CK increased							
n (%) [1]	191 (44.7)	2 (0.9)	93 (21.5)	68 (24.8)	44 (22.9)	2 (1.0)	4 (2.2)
Exposure (months) [2]	1012.9	2017.87	3437.63	2552.25	1996.52	1872.46	1509.45
EAIR [3]	18.86	0.1	2.71	2.66	2.2	0.11	0.26
Alopecia							
n (%) [1]	42 (9.8)	122 (56.2)	50 (11.5)	38 (13.9)	26 (13.5)	107 (55.7)	68 (36.6)
Exposure (months) [2]	1668.7	928.3	3746.14	2737.74	2127.64	861.5	1002.15
EAIR [3]	2.52	13.14	1.33	1.39	1.22	12.42	6.79
Hyperkeratosis							
n (%) [1]	9 (2.1)	89 (41.0)	44 (10.2)	34 (12.4)	27 (14.1)	72 (37.5)	54 (29.0)
Exposure (months) [2]	1817.4	1247.51	3762.99	2758.77	2118.8	1196.52	1103.15
EAIR [3]	0.5	7.13	1.17	1.23	1.27	6.02	4.9
Rash							
n (%) [1]	146 (34.2)	47 (21.7)	58 (13.4)	33 (12.0)	27 (14.1)	41 (21.4)	54 (29.0)

Exposure (months) [2]	1256.18	1608.41	3713.35	2779.56	2121.72	1486.19	1097.1
EAIR [3]	11.62	2.92	1.56	1.19	1.27	2.76	4.92
Oedema peripheral							
n (%) [1]	174 (40.7)	19 (8.8)	54 (12.5)	33 (12.0)	20 (10.4)	15 (7.8)	20 (10.8)
Exposure (months) [2]	1139.22	1823.11	3792.76	2820.27	2206.39	1688.34	1357.11
EAIR [3]	15.27	1.04	1.42	1.17	0.91	0.89	1.47
Palmar-plantar erythrodysaesthesia syndrome							
n (%) [1]	5 (1.2)	112 (51.6)	19 (4.4)	16 (5.8)	13 (6.8)	98 (51.0)	26 (14.0)
Exposure (months) [2]	1840.72	1072.13	3968.85	2923.33	2275.15	1003.6	1372.55
EAIR [3]	0.27	10.45	0.48	0.55	0.57	9.76	1.89
Dermatitis acneiform							
n (%) [1]	177 (41.5)	9 (4.1)	13 (3.0)	10 (3.6)	5 (2.6)	8 (4.2)	8 (4.3)
Exposure (months) [2]	1157.03	1947.96	4076.71	3014.01	2356.96	1811.25	1494.34
EAIR [3]	15.3	0.46	0.32	0.33	0.21	0.44	0.54
Any preferred term							

Combo 450 RP

The most common AEs (≥20% of patients) were nausea (39.4%), diarrhoea (36.1%), fatigue (30.3%), vomiting (26.6%), increased blood CK (24.8%), arthralgia (24.8%) and constipation (22.6%).

Grade 3/4 AEs (≥5% of patients) were increased GGT (8%), hypertension (5.8%) and increased blood CK (5.5%).

AEs requiring dose adjustment or study drug interruption (≥5% of patients) were nausea (6.6%), vomiting (5.8%), increased ALT (5.5%) and decreased ejection fraction (5.1%).

AEs requiring additional therapy (≥10% of patients) were nausea (20.8%), diarrhoea (13.5%) and constipation (12.4%).

Of the 196 patients who received Combo 450 for ≥6 months, 113 (57.7%) reported Grade 3/4 AEs.

AEs reported at a higher incidence (≥10% difference) in patients exposed more than 6 months (n=196) compared with patients exposed less than 6 months (n=78) were diarrhoea (39.8% vs 26.9%), abdominal pain (21.4% vs 2.6%), arthralgia (29.6% vs 12.8%), increased CK (27.6% vs 17.9%), pyrexia (18.9% vs 7.7%) and hyperkeratosis (15.3% vs 5.1%). Other AEs that increased after 6 months treatment (<10% difference) included alopecia (16.3% vs. 7.7%), hypertension (13.3% vs. 6.4%) and decreased ejection fraction (7.7% vs. 3.8%).

No Grade 3-4 AE was reported at a higher incidence (≥2% difference) in patients who received ≥6 months compared those who received < 6 months of study drug.

AEs reported at a lower incidence (≥10% difference) in patients exposed for more than 6 months were increased AST (6.1% vs 17.9%) and ALT (9.2 vs 21.8%).

Of patients exposed for ≥6 months, 171 had a first or worst occurrence of an AE, with 67 patients (34.2%) having Grade 3/4 events. New AEs were reported in the following proprtions of patients: arthralgia (14.8%), diarrhoea (12%), nausea (11.2%) and headache (10.7%). New Grade 3/4 AEs affected <5% of patients; these included increased blood CK (3.1%), anaemia (2.6%) and hypertension (2%).

Enco 300 P

The encorafenib single agent (300 mg orally once daily) safety profile is based on data from 217 patients with unresectable or metastatic BRAF V600-mutant melanoma (hereafter referred to as the pooled encorafenib 300 population). The most common adverse drug reactions (ADRs) (≥25%) reported with

encorafenib 300 were hyperkeratosis, alopecia, PPES, fatigue, rash, arthralgia, dry skin, nausea, myalgia, headache, vomiting and pruritus.

The most common AEs (≥20% of patients) were alopecia (56.2%), palmar plantar erythrodysaesthesia (PPE) syndrome (51.6%), arthralgia (42.9%), hyperkeratosis (41%), nausea (37.8%), dry skin (31.3%), myalgia (29.5%), headache (28.1%), fatigue (27.6%), vomiting (26.7%), palmoplantar keratoderma (23%), decreased appetite (22.6%), insomnia (22.1%), rash (21.7%), pruritus (21.7%) and pain in extremity (20.7%).

Grade 3/4 AEs (≥5% of patients) were PPE (12.4%), arthralgia (9.2%) and myalgia (9.2%).

AEs requiring dose adjustment or study-drug interruption (≥5% of patients) were PPE (22.6%), arthralgia (12%), myalgia (11.5%), nausea (7.8%), hyperkeratosis (7.4%) and headache (5.5%).

AEs requiring additional therapy (≥10% of patients) were nausea (20.8%), diarrhoea (13.5%) and constipation (12.4%).

Of the 122 patients who received Enco 300 for ≥6 months, 81 (66.4%) reported Grade 3/4 AEs.

AEs reported at a higher incidence (≥10% difference) in patients exposed more than 6 months (n=122) compared with patients exposed less than 6 months (n=95) included arthralgia (54.1% vs 28.4%), musculoskeletal pain (21.3 vs 10.5%), alopecia (69.7% vs 38.9%), dry skin (38.5% vs 22.1%) hyperkeratosis (50.8% vs 28.4%), pruritus (26.2% vs 15.8%), palmoplantar keratoderma (30.3% vs 13.7%) and PPE (55.7% vs 46.3%).

Of patients exposed for ≥6 months (n=122), 108 had a first or worst occurrence of an AE, with 37 patients (30.3%) having Grade 3/4 events. Most frequently reported AEs were arthralgia (14.8%), hyperkeratosis (9.8%), and dry skin (7.4%). The only Grade 3/4 AE (≥2 % of patients) was anaemia (2.5%).

In the Combo 450 RP compared to the Enco 300 P population, the incidence of AEs in patients who received ≥6 months of treatment showed a:

• lower incidence of skin disorders including alopecia (16.3% vs 69.7%), hyperkeratosis (15.3% vs 50.8%), PPE (6.6% vs 55.7%), palmoplantar keratoderma (9.7% vs 33.3%) and melanocytic naevus (2% vs 13.9%)

• a higher incidence of blurred vision (16.8% vs 4.1%), abdominal pain (21.4% vs 5.7%), dizziness (15.1% vs 5.3%) and retinopathy (9.2% vs. 0.8%). The incidence of any grade retinopathy with a first or worst occurrence ≥ 6 months after treatment start in the Combo 450 arm was 2.7%.

Vemurafenib

The most common AEs (≥20% of patients) were arthralgia (44.6%), alopecia (36.6%), diarrhoea (33.9%), nausea (33.9%), fatigue (30.6%), rash (29%), hyperkeratosis (29%), pyrexia (28%), photosensitivity reaction (24.2%), keratosis pilaris (23.1%) and dry skin (22.6%).

Other AEs reported in≥10% of patients in the vemurafenib arm and at a higher incidence as compared to the Combo 450 arm included decreased appetite (19.4% vs 8.3%), PPE (16.7% vs 6.8%), skin hyperpigmentation (14.5% vs 1.6%) and sunburn (10.2% vs 0%).

The only Grade 3/4 AE (≥5% of patients) was arthralgia (5.9%).

AEs requiring dose adjustment or study-drug interruption (≥5% of patients) were arthralgia (8.6%), pyrexia (7.5%), nausea (7.5%), rash (7.5%), generalised rash (5.4%) and maculo-papular rash (5.4%).

AEs requiring additional therapy (≥10% patients) were nausea (20.3%), diarrhoea (12.5%), constipation (11.5%) and anaemia (10.4%).

Of the 95 patients who received treatment for ≥6 months, 62 (65.3%) reported Grade 3/4 AEs.

The incidence of AEs with a first or worst occurrence ≥ 6 months was 86.3%; only diarrhoea was reported in ≥ 10% patients (11.8%). Grade 3/4 AEs (≥2% of patients) included general physical health deterioration (3.2%) and keratoacanthoma, central nervous system metastasis and anaemia (all 2.1%).

Based on the updated review, Gamma glutamyl transferase (GGT) increased was identified as meeting the criteria for inclusion as an ADR for both Enco 300 and Combo 450. In addition, Blood creatinine increased and Renal failure, which were already identified as ADRs for Enco 300, were identified as meeting the criteria for inclusion as ADRs for Combo 450.

Table 61: ADRs Reported with a ⩾5% Difference in Incidence Between the Combo 450 RP Population and the Enco 300 P Population or Between the Combo 450 (or Enco 300) and Vemurafenib Arms of Study CMEK162B2301 (Broad Safety Set) (4-month update)

PT	Enco 300 P % Overall (Grade 3-4 %)	Combo 450 RP % overall (Grade 3-4)	Combo 450 arm % overall (Grade 3-4)	Vemurafenib
Skin				
Hyperkeratosis	58. 5(6.0)	20.8 (0.4)	24.0 (0.5)	50.0 (1.1)
Alopecia	57.1 (-)	14.6 (-)	14.6 (-)	37.6 (-)-
PPES	51.6 (12.4)	6.2(0.0)	7.3 (0.0)	14.0 (1.1)
Rash	43.3 (4.6)	19.7 (0.7)	22.9 (1.0)	53.2 (13.4)
Dry skin	37.8 (-)	14.6 (-)	16.7 (-)	26.3 (-)
Pruritus	29.5 (0.5)	12.7 (0.4)	13.5 (0.5)	21.0 (1.1)
Erythema	16.6 (1.4)	8.0 (0.0)	7.8 (0.0)	17.2 (0.5)
Dermatitis acneiform	7.8 (0.0)	4.4 (0.0)	3.1 (0.0)	6.5 (0.0)
Skin exfoliation	6.5 (0.5)	1.1(0.0)	1.6 (0.0)	3.2 (0.0)
Skin hyperpigmentation	10.1 (-)	1.8(-.)	2.6 (-)	2.7 (-)
Panniculitis	0.5 (0.0)	1.5 (0.0)	1.6 (0.0)	3.2 (0.5)
Gastrointestinal Disorders				
Nausea	37.8 (3.7)	41.6 (2.6)	43.2 (1.6)	34.9 (1.6)
Vomiting	27.6 (4.1)	28.1 (2.2)	30.2 (1.6)	16.1 (1.1)
Constipation	16.1 (0.0)	24.1 (0.0)	22.4 (0.0)	6.5 (0.5)
Abdominal pain	15.7 (2.8)	27.4 (2.6)	28.6 (3.6)	16.1 (1.1)
Diarrhoea	12.4 (1.4)	38.0 (3.3)	37.0 (2.6)	34.2 (2.2)
Colitis	0.0 (0.0)	1.8 (0.7)	2.6 (1.0)	0.5 (0)
Pancreatitis	0.5 (0.5)	0.7(0.7)	1.0(1.0)	1.1 (0.5)
Musculoskeletal and Connective Tissue Disorders				
Muscular disorder/ Myopathy-Myalgia	35.9 (9.2)	25.9(0.4)	26.6 (0.5)	22.0 (0.5)
Arthralgia	43.3 (9.2)	27 (0.7)	25.5(0.5)	45.7 (5.9)
Pain in extremity	21.2 (0.9)	10.6 (1.5)	11.5 (1.0)	14.0 (1.1)
Back pain	15.3 (2.3)	10.5 (0.7)	9.9(0.5)	6.5 (1.6)
Arthritis	5.1 (1.8)	1.5 (1.1)	2.1(1.6)	2.2 (0.5)
Rhabdomyolysis	0	0.4 (0.0)	0.5(0.0)	0
Nervous System Disorders				
Headache	29.0 (3.2)	21.4 (1.5)	22.9(1.6)	19.9 (0.5)
Dysgeusia	13.8(0.0)	6.6(0.0)	5.7(0.0)	10.8 (0.0)
Neuropathy	22.6 (1.8)	13.1 (1.1)	12.0(1.0)	13.4 (1.6)

PT	Enco 300 P % Overall (Grade 3-4 %)	Combo 450 RP % overall (Grade 3-4)	Combo 450 arm % overall (Grade 3-4)	Vemurafenib
Facial paresis	7.4 (1.4)	0.7 (0.4)	1.0(0.5)	0.5 (0.0)
Dizziness	6.0 (0.5)	16.3 (2.6)	15.1(2.6)	4.3 (0.0)
General Disorders				
Fatigue	43.8 (2.9)	41.6 (2.9)	43.2(3.1)	46.2 (6.5)
Pyrexia	15.2 (0.9)	17.2 (2.9)	18.2(4.2)	29.6 (0.0)
Oedema peripheral	10.1 (0.0)	15.3 (1.1)	13.5(1.1)	14.5 (1.1)
Investigations				
Transaminases increased	6.5 (1.4)	15.7 (5.5)	13.5(6.3)	10.2(1.6)
GGT increased	11.5 (5.1)	14.6(8.4)	15.1(9.4)	11.3 (3.2)
Blood ALP increased	2.8 (0.0)	7.3 (0.7)	8.3(0.5)	5.4 (1.1)
Lipase increased	2.3 (1.4%)	5.1 (2.6)	2.1 (1.6)	1.6 (1.1)
Blood CK increased	0.9(0.0)	27.0 (5.8)	22.9 (6.8)	2.2 (0.0)
Amylase increased	0.5 (0.0)	3.3 (1.5)	2.1(1.6)	1.1 (1.1)
Blood creatinine increased	2.3(0.0)	6.2(0.7)	6.8 (1.0)	6.5 (1.1)
Eye disorders				
Visual impairment	5.5 (0.0)	21.5 (0.4)	21.4(0.0)	4.3(0.0)
Retinal detachment	1.8(0.0)	29.6 (1.8)	19.8(2.6)	2.2(0.0)
Uveitis	0.5(0.0)	4.4 (0.4)	4.1(0.5)	3.8 (0.0)
Vascular Disorders				
Haemorrhage	11.5(1.8)	17.9 (3.3)	19.3(3.6)	8.6(1.6)
Hypertension	5.1(2.8)	11.7 (5.5)	11.5(5.2)	11.8(3.2)
Venous Thromboembolism	2.8 (0.5)	4.7 (0.7)	5.7(1.6)	2.2(1.1)
Blood and Lymphatic System Disorders				
Anaemia	7.4 (2.3)	19.7 (4.7)	16.7(4.7)	10.2(2.7)
Immune system disorders				
Drug hypersensitivity	4.1 (0.5)	3.3 (0.0)	3.6(0.0)	4.8(1.6)
Cardiac disorders				
Left ventricular dysfunction	1.8 (0.9)	8.4(1.1)	7.8(1.6)	0.5(0.0)
Supraventricular tachycardia	4.1(0.9)	1.8(0.0)	2.1(0.0)	4.3(0.5)
Metabolic disorders				
Decreased appetite	22.1(0.5)	7.7(0.0)	8.3(0.0)	19.4(0.0)
Psychiatric disorders				
Insomnia	22.1(2.8)	8.4(0.0)	9.4(0)	8.1(0.0)
Skin neoplasm and malignancies				
Melanocytic neavus	10.6(-)	1.5(0.0)	1.6(0.0)	3.8(0.0)
Skin papilloma	10.6(0.0)	6.9(0.0)	8.9(0.0)	19.4(0.0)
Squamous Cell Carcinoma	6.9(0.0)	3.3(0.0)	3.6(0.0)	17.2(7.0)
Basal cell carcinoma	0.9(0.0)	1.1(0.0)	1.6(0.0)	2.2(0.0)
New primary melanoma	4.1(1.0)	0.4 (0.4)	0.5(0.5)	2.7(1.1)
Renal and urinary disorders				
Renal failure	2.8(1.4)	3.3(2.2)	4.2(3.1)	4.8(1.6)

Source ISS-Part 1_u Tables: 2.6.1.a, 2.6.1.b, 2.6.2.1.a, 2.6.2.1.b

Very common ADRs with a ≥10% incidence difference and common ADR with a ≥5% incidence difference between Combo 450 RP and Enco 300 P are highlighted in green

Very common ADRs with a ≥10% incidence difference and common ADR with a ≥5% incidence difference between Combo 450arm and Vemurafenib are highlighted in blue

Encorafenib specific ADR not considered for the Combo 450

Table 62: Adverse reactions

		Encorafenib single agent 300 mg (n=217)		Encorafenib 450 mg in combination with binimetinb (n=274)	
System Organ Class	**Adverse reaction**	**Frequency (All grades) n (%)**	**Frequency (Grade 3-4) n (%)**	**Frequency (All grades) n (%)**	**Frequency (Grade 3-4) n (%)**
Neoplasms benign, malignant and unspecified	CuSCC	16 (7.4)	0	9 (3.3)	1 (0.4)
	Basal cell carcinoma	2 (0.9)	1 (0.5)	3 (1.1)	0
	Skin papilloma	25 (11.5)	0	22 (8.0)	0
	Melanocytic naevus	23 (10.6)	0		
	New Primary Melanoma	9 (4.1)	2 (0.9)		
Blood and lymphatic system disorders	Anaemia			54 (19.7)	13 (4.7)
Immune system disorders	Hypersensitivity	8 (3.7)	1 (0.5)	9 (3.3)	0
Metabolism and nutrition disorders	Decreased appetite	48 (22.1)	1 (0.5)		
Psychiatric disorders	Insomnia	48 (22.1)	6 (2.8)		
Nervous system disorders	Neuropathy peripheral	49 (22.6)	4 (1.8)	36 (13.1)	3 (1.1)
	Dizziness			42 (15.3)	7 (2.6)
	Headache	64 (29.5)	7 (3.2)	59 (21.5)	4 (1.5)
	Dysgeusia	30 (13.8)	0	18 (6.6)	0
	Facial paresis	16 (7.4)	3 (1.4)	2 (0.7)	1 (0.4)
Eye disorders	Visual impairment			59 (21.5)	1 (0.4)
	RPED			81 (29.6)	5 (1.8)
	Uveitis	1 (0.5)	0	12 (4.4)	1 (0.4)
Cardiac disorders	Left ventricular dysfunction			23 (8.4)	3 (1.1)
	Supraventricular tachycardia	9 (4.1)	2 (0.9)		
Vascular disorders	Haemorrhage			49 (17.9)	9 (3.3)
	Hypertension			32 (11.7)	15 (5.5)
	VTE			13 (4.7)	3 (1.1)

Gastrointestinal disorders	Abdominal pain			75 (27.4)	7 (2.6)
	Diarrhoea			104 (38.0)	9 (3.3)
	Vomiting	60 (27.6)	9 (4.1)	77 (28.1)	6 (2.2)
	Nausea	82 (37.8)	8 (3.7)	114 (41.6)	7 (2.6)
	Constipation	37 (17.1)	0	66 (24.1)	0
	Colitis			6 (2.2)	2 (0.7)
	Pancreatitis	1 (0.5)	1 (0.5)	2 (0.7)	2 (0.7)
Skin and subcutaneous tissue disorders	Hyperkeratosis	127 (58.5)	13 (6.0)	57 (20.8)	1 (0.4)
	Rash	94 (43.3)	10 (4.6)	54 (19.7)	2 (0.7)
	Dry skin	82 (37.8)	0	40 (14.6)	0
	Pruritus	64 (29.5)	1 (0.5)	32 (11.7)	1 (0.4)
	Alopecia	124 (57.1)	0	40 (14.6)	0
	Photosensitivity	9 (4.1)	0	11 (4.0)	1 (0.4)
	Dermatitis acneiform	17 (7.8)	0	12 (4.4)	0
	PPES	112 (51.6)	27 (12.4)	17 (6.2)	0
	Erythema	37 (17.1)	3 (1.4)	22 (8.0)	0
	Panniculitis			4 (1.5)	0
	Skin hyperpigmentation	22 (10.1)	0		
	Skin exfoliation	14 (6.5)	1 (0.5)		
Musculoskeletal and connective tissue disorders	Arthralgia	94 (43.3)	20 (9.2)	74 (27.0)	2 (0.7)
	Muscular disorders/Myalgia	78 (35.9)	20 (9.2)	71 (25.9)	2 (0.7)
	Back pain	33 (15.2)	5 (2.3)	30 (10.9)	2 (0.7)
	Pain in extremity	46 (21.2)	2 (0.9)	29 (10.6)	4 (1.5)
	Arthritis	11 (5.1)	3 (1.4)		
	Rhabdomyolysis			1 (0.4)	1 (0.4)
Renal and urinary disorders	Renal failure	6 (2.8)	3 (1.4)	9 (3.3)	6 (2.2)
General disorders and administration site conditions	Pyrexia	33 (15.2)	2 (0.9)	47 (17.2)	8 (2.9)
	Peripheral oedema			42 (15.3)	3 (1.1)
	Fatigue	95 (43.8)	10 (4.6)	120 (43.8)	8 (2.9)
Investigations	Blood creatine phosphokinase increased			74 (27.0)	16 (5.8)
	Transaminase increased	14 (6.5)	3 (1.4)	43 (15.7)	15 (5.5)
	Gamma-glutamyl transferase increased	25 (11.5)	11 (5.1)	40 (14.6)	23 (8.4)
	Blood creatinine increased	5 (2.3)	0	17 (6.2)	2 (0.7)
	Blood alkaline phosphatase increased			20 (7.3)	2 (0.7)
	Amylase increased	1 (0.5)	0	9 (3.3)	4 (1.5)
	Lipase increased	5 (2.3)	3 (1.4)	14 (5.1)	7 (2.6)

Adverse events of special interest (AESI) were identified based on the known class effects of BRAF (encorafenib) and MEK (binimetinib) inhibitors.

Class effects of BRAF inhibitors include cutaneous malignancies (mostly squamous cell carcinoma and new primary melanoma), cutaneous papilloma, arthralgia, skin toxicities including rash, hyperkeratosis, palmar-plantar erythrodysaesthesia (PPE) syndrome and QTc prolongation.

Class effects of MEK inhibitors include ocular toxicities, elevations of CK, left ventricular dysfunction, skin toxicities including rash and acneiform dermatitis, hypertension, venous thromboembolic events (VTEs), diarrhoea, interstitial lung disease, oedema and haemorrhage.

The AESI groupings for each component of Combo 450 RP were reported and analysed as follows in the initial MAA:

Common to Both	**Specific to encorafenib**	**Specific to binimetinib**
Ocular: retinopathy excluding RVO, RVO, uveitis-type events Hepatic: LFT abnormalities, hepatic failure Myopathy/rhabdomyolysis-related Dermatologic: rash, skin infections, photosensitivity, nail disorders, PPE, severe cutaneous adverse reactions	Tachycardia Acute renal failure Facial paresis Cutaneous malignancies: SCC, non-SCC, melanomas	Cardiac: bradycardia, left ventricular dysfunction Hypertension Peripheral oedema Haemorrhage Venous thromboembolism Pneumonitis

Cutaneous malignancies

Cutaneous squamous cell carcinoma

In the pooled Combo 450 population, cuSCC including keratoacanthomas was observed in 3.3% (9/274) of patients. The median time to onset of the first event of cuSCC (all grades) was 6.5 months (range 1.0 to 22.8 months).

In the pooled encorafenib 300 population, cuSCC was reported in 7.4% (16/217) patients. For patients in the Phase III study (CMEK162B2301) who developed cuSCC, the median time to onset of the first event of cuSCC (all grades) was 2.3 months (range 0.3 to 12.0 months).

New primary melanoma

In the pooled encorafenib 300 population, new primary melanoma events occurred in 4.1% of patients (9 /217) and was reported as Grade 1 in 1.4% (3/217) of patients, Grade 2 in 2.1% (4/217) of patients, Grade 3 in 0.5% (1/217) of patients and Grade 4 in 0.5% (1/217) of patients.

Ocular events

In the pooled Combo 450 population, uveitis was reported in 4.4% (12/274) of patients, and was Grade 1 in 0.4% (1/274), Grade 2 in 3.6% (10/274) and Grade 3 in 0.4% (1/274). Visual impairment, including blurred vision and reduced visual acuity, occurred in 21.5% (59/274) of patients. Uveitis and visual impairment were generally reversible.

RPED occurred in 29.6% (81/274) of patients, most of them had Grade 1-2 and 1.8% (5/274) had Grade 3 events.

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.

Left ventricular dysfunction

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

Haemorrhage

Haemorrhagic events were observed in 17.9% (49/274) of patients in the pooled Combo 450 population. Most events were Grade 1 or 2 (14.6%) and 3.3% were Grade 3-4 events. Few patients required 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 was reported 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.*

Hypertension

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

Venous thromboembolism

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

Pancreatitis

Pancreatic enzyme elevation, mostly asymptomatic, was reported in the pooled Combo 450 population. Amylase and lipase elevations were reported in 3.3% (9/274) and 5.1% (14/274) of patients, respectively. Pancreatitis was reported in 0.7% (2/274) of patients. Both patients experienced Grade 3 events. Pancreatitis led to dose interruption or adjustment in (0.4 %) 1/274 of patients.

Dermatologic reactions

Rash

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 discontinuation in 0.4% (1/274) patients and to dose interruption or dose modification in 1.1% (3/274) of patients.

In the pooled encorafenib 300 population, rash was reported in 43.3% (94/217) of patients. Most events were mild, with Grade 3 or 4 events reported in 4.6% (10/217) of patients. Rash led to discontinuation in 0.5% (1/217) of patients and to dose interruption or dose modification in 7.4% (16/217) of patients.

Palmar-plantar erythrodysaesthesia syndrome (PPES)

PPES was reported in 6.2% (17/274) of patients in the pooled Combo 450 population. All the PPES adverse reactions were either Grade 1 (3.3%) or Grade 2 (2.9%). Dose interruption or dose modification occurred in 1.1% (3/274) of patients.

In the Combo 300 arm in Part 2 of the pivotal study, PPES was observed in 3.9% (10/257) of patients with Grade 3 reported in 0.4% (1/257) of patients.

In the pooled encorafenib 300 population, PPES was reported in 51.6% (112/217) of patients. Most events were mild-moderate: Grade 1 in 12.4% (27/217) of patients, Grade 2 in 26.7% (58/217) and Grade 3 in 12.4% (27/217) of patients. PPES led to discontinuation in 4.1% (9/217) of patients and to dose interruption or dose modification in 23.0% (50/217) of patients.

Dermatitis acneiform

Dermatitis acneiform was reported when encorafenib is used in combination with binimetinib (see section 4.8 of binimetinib SmPC).

Photosensitivity

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.

In the pooled encorafenib 300 population, photosensitivity was reported in 4.1% (9/217) of patients. All events were Grade 1-2. No event required discontinuation, dose modification or interruption.

Facial paresis

In the pooled Combo 450 population, facial paresis occurred in 0.7% (2/274) of patients including Grade 3 in 0.4% (1/274) of patients. The events were reversible, and no event led to treatment discontinuation. Dose interruption or modification was reported in 0.4% (1/274) of patients.

In the pooled encorafenib 300 population, facial paresis was observed in 7.4% (16/217) of patients. Most events were mild-moderate: Grade 1 in 2.3% (5/217); Grade 2 in 3.7% (8/217) and Grade 3 in 1.4% (3/217) of patients. The median time to onset of the first event of facial paresis was 0.3 months (range 0.1 to 12.1 months). Facial paresis was generally reversible and led to treatment discontinuation in 0.9% (2/217). Dose interruption or modification was reported in 3.7% (8/217) and symptomatic treatment including corticosteroids was reported in 5.1% (11/217) of patients.

CK elevation and rhabdomyolysis

CK elevation and rhabdomyolysis occurred when encorafenib is used in combination with binimetinib (see section 4.8 of binimetinib SmPC).

Renal dysfunction

In the pooled Combo 450 population, mild, mostly Grade 1, asymptomatic blood creatinine elevation was noted in 6.2% (17/274) of patients treated with the Combo 450 mg. The incidence of Grade 3 or 4 elevation was 0.7% (2/274). Renal failure events, including acute kidney injury and renal impairment, were reported in 3.3% (9/274) patients treated with encorafenib and binimetinib with Grade 3 or 4 events in 2.2% (6/274) of

patients. Renal failure was generally reversible with dose interruption, rehydration and other general supportive measures.

Liver laboratory abnormality

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 incidence of liver laboratory abnormalities was:

- 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)

Gastrointestinal disorders

In the pooled Combo 450 population, diarrhoea was observed in 38% (104/274) of patients and was Grade 3-4 in 3.3% (9/274) 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.

Anaemia

In the pooled Combo 450 population, anaemia was reported in 19.7% (54/274) of patients; 4.7% (13/274) patients had a 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.

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.

Cardiac Electrophysiology

In the safety analysis of pooled studies, 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 Sections 4.2 and 4.4).

Serious adverse event / deaths / other significant events

Deaths

The incidence of on-treatment deaths was similar in the Combo 450 RP and the Enco 300 P populations (8.4% vs 6.9%, with an EAIR of 0.74 deaths per 100 patient–months in both populations).

Most deaths were due to progression of malignant melanoma (5.8% Combo 450 vs 5.5% Enco 300 P).

In the Combo 450 RP population, on-treatment deaths due to events other than disease progression included AEs by PT of multiple organ dysfunction syndrome, cerebral haemorrhage (in the context of brain metastasis), completed suicide, euthanasia, myocardial infarction, reported in 1 patient each, and AEs of death, reported in 2 patients; 0.7% of deaths were attributed to related AEs.

Adverse events resulting in death for patients in the Enco 300 P population were reported under the PTs of myocardial infarction, unknown cause, general physical health deterioration and pneumonia (1 patient each); 0.5% of deaths were attributed to related AEs.

At the four month safety update, the overall incidence of on-treatment deaths (with or without adjustment for study drug exposure) was higher in the Combo 450 RP than in Enco 300 P populations (10.2% vs 7.4%), with similar EAIRs (as per the initial MAA) of 0.73 vs 0.71 deaths per 100 patient-months respectively. Most deaths remained due to progression of malignant melanoma (7.7% Combo 450 vs 6.0% Enco 300 P).

Table 63: On-treatment Deaths by Preferred Term and Treatment (Broad Safety Set) – Updated MAA (9 November 2016)

	Melanoma				Study CMEK162B2301		
Primary system organ class 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)	16 (7.4)	50 (11.5)	28 (10.2)	19 (9.9)	15 (7.8)	19 (10.2)
Acute myocardial infarction	0	1 (0.5)	0	0	0	1 (0.5)	0
Myocardial infarction	0	0	1 (0.2)	0	0	0	0
Death	0	1 (0.5)	3 (0.7)	2 (0.7)	2 (1.0)	1 (0.5)	0
Euthanasia	1 (0.2)	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
Disease progression	0	0	1 (0.2)	0	0	0	0
Multi-organ failure	1 (0.2)	0	0	0	0	0	0
Intestinal sepsis	0	0	0	0	0	0	1 (0.5)
Pneumonia	0	1 (0.5)	0	0	0	0	0
Sepsis	2 (0.5)	0	0	0	0	0	0
Malignant melanoma	40 (9.4)	13 (6.0)	34 (7.9)	21 (7.7)	12 (6.3)	13 (6.8)	18 (9.7)
Metastases to central nervous system	0	0	1 (0.2)	1 (0.4)	1 (0.5)	0	0
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
Neoplasm progression	0	0	1 (0.2)	0	0	0	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
Dyspnoea	1 (0.2)	0	0	0	0	0	0
Embolism	1 (0.2)	0	0	0	0	0	0

Serious Adverse Events

Table 64: Serious Adverse Events, Regardless of Study Drug Relationship, by Preferred Term and Treatment - Overall and Maximum Grade 3 or 4 (≥2% in any population) – initial MAA

	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)
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
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
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)
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)
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

The incidence of SAEs was similar in the different treatment groups: 35.8%, 31.8% and 37.1% of patients in Combo 450 RP, Enco 300 P group and the vemurafenib arm of the Phase 3 study, respectively. The median time to first SAE for the Enco 300 P population was shorter than the Combo 450 RP population (1.8 months [95% CI: 0.4, 2.9] vs 3.8 months [95% CI: 3.2, 4.9]).

In the Combo 450 arm of Study CMEK162B2301 Part 1 SAEs were reported most frequently (> 5.0% of patients) under the SOCs of gastrointestinal disorders (9.4%), infections and infestations (8.9%), general disorders and administration site conditions (8.3%) and nervous system disorders (7.3%).

For the Combo 450 RP population, SAEs reported more frequently by PT were pyrexia, pneumonia and nausea (2.2% each), for the Enco P population they were nausea and vomiting (2.8% each) and in the vemurafenib arm of Study B2301 SAEs were reported most frequently under the PT of general physical health deterioration (3.2%).

SAEs by duration of exposure reflected the unadjusted rate of SAEs, being marginally higher for Combo 450 RP than Enco 300 P (3.91 vs. 3.50 per 100 patient-months, respectively). The most common PTs were similar for EAIR adjusted and non-adjusted rates; for Combo 450 RP the most common exposure adjusted SAEs

were nausea, pneumonia and pyrexia (0.16 per 100 patient-months each), anaemia and vomiting (0.13 per 100 patient-months each) and diarrhoea (0.11 per 100 patient-months). This was followed by abdominal pain, acute kidney injury, cerebral haemorrhage and general physical health deterioration (all 0.10 per 100 patient-months).

For the Enco 300 P population, the most common SAE PTs by EAIR were nausea and vomiting (0.27 per 100 patient-months each), back pain, CNS metastases and pain (0.18 per 100 patient-months each), facial paralysis, hyperglycaemia, myalgia and pyrexia (0.14 per 100 patient-months each) and dehydration and musculoskeletal pain (0.13 per 100 patient-months each).

In the 4-month safety update in the Combo 450 RP, the overall incidence of SAEs regardless of study drug relationship increased from 35.8% (grade 3-4, 31.8%) at the time of the initial MAA to 40.1% (grade 3-4, 34.3%). No SAEs were reported under new SOCs in ≥10% of patients or new PTs in ≥2% of patients in the impacted populations as compared to the initial MAA.

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 65: 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)

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		
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)

Source Safety Appendix: Q96E T.1.1
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.

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 (≥25%) occurring in patients treated with encorafenib 300 mg administered with binimetinib were fatigue, nausea and diarrhoea.

AEs more frequent in the Combo 450 arm are shown in Table 66 and those more frequent in the Combo 300 arm are shown in Table 67. The EAIR values were consistent with the imbalances in AE incidences between the Combo 450 vs the Combo 300 arm.

Table 66: 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 67: 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 68: 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

Table 69: Newly occurring or worsening haematology abnormalities based on CTCAE Grade

	Melanoma			Study CMEK162B2301 Part 1		
Parameter Worsened grade	Binimetinib 45 mg BID N=427 n/m (%)	Encorafenib 300 mg QD N=217 n/m (%)	Combo 450 mg QD N=274 n/m (%)	Combo 450 mg QD N=192 n/m (%)	Encorafenib 300 mg QD N=192 n/m (%)	Vemurafenib N=186 n/m (%)
Hemoglobin low (g/L)						
Grade 1	128/272 (47.1)	59/155 (38.1)	61/190 (32.1)	43/140 (30.7)	54/138 (39.1)	46/127 (36.2)
Grade 2	57/401 (14.2)	19/208 (9.1)	27/258 (10.5)	20/184 (10.9)	14/183 (7.7)	13/177 (7.3)
Grade 3	12/415 (2.9)	3/210 (1.4)	12/269 (4.5)	7/187 (3.7)	3/185 (1.6)	4/181 (2.2)
Grade 4	0/415	0/210	0/269	0/187	0/185	0/182
Hemoglobin high (g/L)						
Grade 1	2/415 (0.5)	6/210 (2.9)	4/269 (1.5)	1/187 (0.5)	5/185 (2.7)	8/182 (4.4)
Grade 2	0/415	0/210	0/269	0/187	0/185	0/182
Grade 3	0/415	0/210	0/269	0/187	0/185	0/182
Grade 4	0/415	0/210	0/269	0/187	0/185	0/182
Leukocytes low (10^9/L)						
Grade 1	46/392 (11.7)	7/204 (3.4)	28/255 (11.0)	17/183 (9.3)	5/181 (2.8)	14/179 (7.8)
Grade 2	9/410 (2.2)	2/209 (1.0)	10/259 (3.9)	8/186 (4.3)	2/184 (1.1)	3/182 (1.6)
Grade 3	0/415	0/210	0/260	0/187	0/185	1/182 (0.5)
Grade 4	0/415	0/210	0/260	0/187	0/185	0/182
Lymphocytes low (10^9/L)						
Grade 1	43/256 (16.8)	18/191 (9.4)	17/221 (7.7)	5/177 (2.8)	15/179 (8.4)	14/171 (8.2)
Grade 2	33/308 (10.7)	16/198 (8.1)	26/244 (10.7)	16/179 (8.9)	12/179 (6.7)	30/174 (17.2)
Grade 3	21/339 (6.2)	3/207 (1.4)	6/255 (2.4)	4/187 (2.1)	2/185 (1.1)	11/180 (6.1)
Grade 4	2/344 (0.6)	0/207	0/256	0/187	0/185	1/182 (0.5)
Lymphocytes high (10^9/L)						
Grade 1	0/343	0/206	0/254	0/185	0/184	0/181
Grade 2	28/343 (8.2)	11/206 (5.3)	15/254 (5.9)	14/185 (7.6)	9/184 (4.9)	5/181 (2.8)
Grade 3	1/345 (0.3)	0/207	0/256	0/187	0/185	0/182
Grade 4	0/345	0/207	0/256	0/187	0/185	0/182
Neutrophils low (10^9/L)						
Grade 1	30/357 (8.4)	7/204 (3.4)	13/253 (5.1)	11/186 (5.9)	5/182 (2.7)	6/181 (3.3)
Grade 2	9/362 (2.5)	2/205 (1.0)	13/256 (5.1)	8/187 (4.3)	2/183 (1.1)	2/182 (1.1)
Grade 3	3/362 (0.8)	1/206 (0.5)	6/256 (2.3)	4/187 (2.1)	1/184 (0.5)	0/182
Grade 4	0/362	1/207 (0.5)	2/256 (0.8)	2/187 (1.1)	1/185 (0.5)	1/182 (0.5)
Platelets low (10^9/L)						
Grade 1	53/403 (13.2)	9/204 (4.4)	23/267 (8.6)	16/186 (8.6)	6/181 (3.3)	5/179 (2.8)
Grade 2	3/413 (0.7)	0/209	3/269 (1.1)	1/187 (0.5)	0/184	1/182 (0.5)
Grade 3	1/413 (0.2)	1/209 (0.5)	0/269	0/187	1/184 (0.5)	0/182
Grade 4	1/413 (0.2)	0/209	2/269 (0.7)	1/187 (0.5)	0/184	0/182

No new or worsened haematology abnormality was reported at a higher or lower incidence (≥5% difference for any CTCAE Grade) in the Combo 450 RP population than the Enco 300 P population. Most common in all populations was decreased haemoglobin, mainly Grade 1 (Grade 1: 38.1% vs 32.1% of patients, respectively; Grade 2: 9.1% vs 10.5%; Grade 3: 1.4% vs 4.5%; Grade 4: none). No patients discontinued Combo 450 mg due to anaemia, 1.5% required dose adjustment or study drug interruption and 9.5% patients required additional therapy.

Decreased neutrophil count was reported in a higher proportion of patients in the Combo 450 arm of Study CMEK162B2301 vs the Enco 300 and vemurafenib arms: 13% vs 4.7% vs 4.8%, respectively with Grade 3/4 abnormalities reported in 3.1% vs 1% vs 0.5%, respectively.

Biochemistry

In the Enco 300 P and Combo 450 RP populations, increased creatinine was the most common new or worsened biochemistry abnormality, mainly Grade 1 (Grade 1: 71.3% vs 79.2% of patients, respectively; Grade 2: 9% vs 15.2%; Grade 3: 0.5% vs 3%; Grade 4: none). More patients in the Combo 450 RP population had a worsening of post-baseline creatinine by ≥2 grades (17.3% vs 9.5%).

In the Combo 450 RP population, hepatic laboratory values of >3 x ULN increases in ALT occurred in 9.7% of patients and >3 x ULN increases in ALT or AST occurred in 4.3% of patients. The median time to first onset was 29.0 days [range 1-534 days]. In the Enco 300 P population, no common newly occurring notable hepatic laboratory values were reported in ≥5% of patients for any class.

Table 70: Newly Occurring or Worsening Biochemistry Abnormalities Based on CTCAE Grade in ⩾ 10.0% of Patients in the Combo 450 Arm of Study CMEK162B2301 Part 1 (Restricted Safety Set, Part 1)

	Melanoma			Study CMEK162B2301 Part 1		
Parameter Worsened grade	Binimetinib 45 mg BID N=427 n/m (%)	Encorafenib 300 mg QD N=217 n/m (%)	Combo 450 mg QD N=274 n/m (%)	Combo 450 mg QD N=192 n/m (%)	Encorafenib 300 mg QD N=192 n/m (%)	Vemurafenib N=186 n/m (%)
Sodium low (mmol/L)						
Grade 1	41/397 (10.3)	26/206 (12.6)	39/258 (15.1)	27/179 (15.1)	18/184 (9.8)	26/172 (15.1)
Grade 2	0/413	0/211	0/268	0/186	0/186	0/181
Grade 3	11/413 (2.7)	3/211 (1.4)	7/268 (2.6)	7/186 (3.8)	1/186 (0.5)	1/181 (0.6)
Grade 4	0/415	0/211	0/268	0/186	0/186	0/183
ALT high (U/L)						
Grade 1	156/382 (40.8)	25/206 (12.1)	57/242 (23.6)	40/173 (23.1)	21/183 (11.5)	42/176 (23.9)
Grade 2	16/414 (3.9)	6/210 (2.9)	12/268 (4.5)	5/187 (2.7)	5/185 (2.7)	4/182 (2.2)
Grade 3	12/416 (2.9)	3/210 (1.4)	14/269 (5.2)	11/187 (5.9)	3/185 (1.6)	4/183 (2.2)
Grade 4	1/416 (0.2)	0/210	0/269	0/187	0/185	0/183
Alkaline phosphatase high (U/L)						
Grade 1	72/299 (24.1)	26/194 (13.4)	51/230 (22.2)	33/161 (20.5)	22/171 (12.9)	58/157 (36.9)
Grade 2	14/336 (4.2)	6/210 (2.9)	9/264 (3.4)	6/185 (3.2)	5/185 (2.7)	4/180 (2.2)
Grade 3	8/343 (2.3)	0/210	4/267 (1.5)	1/186 (0.5)	0/185	4/183 (2.2)
Grade 4	0/345	0/210	0/269	0/187	0/185	0/183
AST high (U/L)						
Grade 1	263/379 (69.4)	22/205 (10.7)	63/251 (25.1)	39/181 (21.5)	18/182 (9.9)	40/177 (22.6)
Grade 2	23/412 (5.6)	3/210 (1.4)	8/267 (3.0)	7/186 (3.8)	3/185 (1.6)	2/183 (1.1)
Grade 3	11/414 (2.7)	1/210 (0.5)	8/269 (3.0)	5/187 (2.7)	1/185 (0.5)	3/183 (1.6)
Grade 4	1/415 (0.2)	0/210	0/269	0/187	0/185	0/183
CK high (U/L)						
Grade 1	140/397 (35.3)	5/191 (2.6)	111/257 (43.2)	77/177 (43.5)	5/171 (2.9)	6/168 (3.6)
Grade 2	93/410 (22.7)	1/199 (0.5)	39/264 (14.8)	24/182 (13.2)	1/178 (0.6)	1/173 (0.6)
Grade 3	60/413 (14.5)	0/199	9/264 (3.4)	8/182 (4.4)	0/178	0/174
Grade 4	36/413 (8.7)	0/199	2/264 (0.8)	2/182 (1.1)	0/178	0/174
Creatinine high (µmol/L)						
Grade 1	291/366 (79.5)	149/209 (71.3)	206/260 (79.2)	142/183 (77.6)	132/185 (71.4)	122/181 (67.4)
Grade 2	22/415 (5.3)	19/211 (9.0)	41/269 (15.2)	29/187 (15.5)	14/186 (7.5)	47/183 (25.7)
Grade 3	2/416 (0.5)	1/211 (0.5)	8/269 (3.0)	7/187 (3.7)	1/186 (0.5)	2/183 (1.1)
Grade 4	3/416 (0.7)	0/211	0/269	0/187	0/186	0/183
Fasting glucose high (mmol/L)						
Grade 1	10/25 (40.0)	43/168 (25.6)	35/183 (19.1)	27/153 (17.6)	38/149 (25.5)	23/128 (18.0)
Grade 2	2/25 (8.0)	8/181 (4.4)	21/197 (10.7)	16/164 (9.8)	6/159 (3.8)	9/135 (6.7)
Grade 3	0/25	7/187 (3.7)	10/202 (5.0)	9/169 (5.3)	6/164 (3.7)	4/138 (2.9)
Grade 4	0/26	2/187 (1.1)	1/204 (0.5)	1/171 (0.6)	2/164 (1.2)	1/140 (0.7)

GGT high (U/L)						
Grade 1	32/207 (15.5)	39/156 (25.0)	43/197 (21.8)	36/145 (24.8)	35/145 (24.1)	44/144 (30.6)
Grade 2	11/239 (4.6)	20/192 (10.4)	41/238 (17.2)	29/172 (16.9)	17/179 (9.5)	10/170 (5.9)
Grade 3	8/249 (3.2)	16/196 (8.2)	35/254 (13.8)	22/184 (12.0)	15/182 (8.2)	7/174 (4.0)
Grade 4	0/258	3/200 (1.5)	2/261 (0.8)	0/186	3/185 (1.6)	2/183 (1.1)
Magnesium high (mmol/L)						
Grade 1	2/411 (0.5)	31/206 (15.0)	19/266 (7.1)	18/184 (9.8)	29/181 (16.0)	48/179 (26.8)
Grade 2	0/412	0/211	0/269	0/187	0/186	0/183
Grade 3	1/412 (0.2)	2/211 (0.9)	2/269 (0.7)	2/187 (1.1)	0/186	1/183 (0.5)
Grade 4	0/413	0/211	0/269	0/187	0/186	0/183

There were too few patients in the Enco 300 P population with notable hepatic laboratory values and even fewer patients with baseline liver metastases to detect a difference in notable hepatic laboratory values. An assessment of the larger number of patients in the Combo 450 RP population revealed no increase in notable hepatic laboratory values in the patients with liver metastases as compared with patients without liver metastases.

Table 71: Summary of Patients with Newly Occurring Notable Hepatic Laboratory Values

	Melanoma			Study CMEK162B2301		
Variable	Binimetinib 45 mg BID N=427 n/m (%)	Encorafenib 300 mg QD N=217 n/m (%)	Combo 450 mg QD N=274 n/m (%)	Combo 450 mg QD N=192 n/m (%)	Encorafenib 300 mg QD N=192 n/m (%)	Vemurafenib N=186 n/m (%)
ALT > 5 × ULN	13/416 (3.1)	3/210 (1.4)	14/269 (5.2)	11/187 (5.9)	3/185 (1.6)	4/183 (2.2)
AST > 5 × ULN	12/413 (2.9)	1/210 (0.5)	8/269 (3.0)	5/187 (2.7)	1/185 (0.5)	3/183 (1.6)
ALT or AST (AT) > 5 × ULN	17/413 (4.1)	3/210 (1.4)	16/269 (5.9)	12/187 (6.4)	3/185 (1.6)	4/183 (2.2)
Total bilirubin (TBL) > 2 × ULN	5/412 (1.2)	0	1/267 (0.4)	1/185 (0.5)	0	6/183 (3.3)
ALP > 3 × ULN	14/337 (4.2)	5/210 (2.4)	7/265 (2.6)	3/185 (1.6)	4/185 (2.2)	6/182 (3.3)
ALT or AST (AT) and TBL						
AT > 3 × ULN &TBL > 2 × ULN	2/413 (0.5)	0	1/268 (0.4)	1/186 (0.5)	0/185	2/183 (1.1)
ALP and TBL						
ALP > 3 × ULN & TBL > 2 × ULN	1/342 (0.3)	0	0	0	0	1/183 (0.5)
ALT or AST and TBL and ALP						
AT > 3 × ULN & TBL > 2 × ULN & ALP < 2 × ULN [a]	1/340 (0.3) [b]	0	0	0	0	1/183 (0.5) [c]

No cases meeting the case-finding criteria of Hy's law were identified in the Combo 450 RP or Enco 300 P populations. As per the 4-month safety update, no new cases of hepatic events fulfilling the Hy's Law criteria was identified in any patient within the same investigated population.

In the Combo 450 RP population 2 patients had Grade 4 CK elevation, which resolved in 0.3 and 1.0 months respectively. A total of 47/259 (18.1%) patients with baseline Grade 0/1 CK level had a ≥2-grade increase. In the subgroup of patients using statins this proportion was 3/24 (12.5%) with no increases to Grade 3/4 levels. In the Enco 300 P population and the vemurafenib arm of the trial no patients were reported with Grade 4 CK elevation. None of the 15 patients who experienced *left ventricular dysfunction* AESI events had concomitant CK elevations, thus no blood samplings for CK isoenzymes and troponin I were undertaken as per study protocol. However, the presented results regarding elevations / shifts of CK values (including

isoenzymes) argue in favour of skeletal muscle cell damage-induced elevations of CK with no evidence of cardiac damage in the Combo 450 arm.

Increased blood glucose was recorded across the treatment arms with an incidence of Grade 3/4 of 5.5%, 4.8% and 3.6% for Combo 450 RP, Enco 300 P and vemurafenib respectively.

The incidence of newly occurring or worsening proteinuria was similar in the Enco 300 P and Combo 450 RP populations for both Grade 1 and 2 values (Grade 1: 5.4% vs 8%, Grade 2: 3.7% vs 2.9%).

Blood pressure (BP)

Newly abnormal BP values were reported with a higher incidence (≥5% difference) in Combo 450 RP than the Enco 300 P population for both systolic (15.5% vs 8.6%) and diastolic BP (11% vs 2.9%). This corresponds with a higher incidence of hypertension AESIs in the Combo 450 RP vs Enco 300 P population (12% vs. 5.5%).

Electrocardiogram (QTc Effects)

In Study CMEK162B2301, QTcF increases by >60 ms were observed in 5.4%, 3.9% and 5.6% of patients in the Combo 450, Enco 300 and vemurafenib arms, respectively, QTcF increases by >30ms were observed in 26.9%, 29.1% and 42.5% of patients, respectively and new QTcF values >500 ms were observed in 0.5%, 2.8% and 1.7% of patients, respectively.

Left Ventricular Ejection Fraction (LVEF)

Mean worst absolute change in LVEF from baseline was similar in the Enco 300 P and Combo 450 RP populations (4.6% vs 5.9%), as was mean worst LVEF value (61.1% [SD 5.9%] vs. 58.1% [5.6%], respectively). However, more patients in the Combo 450 RP than in the Enco 300 P population experienced a CTCAE Grade 0 to Grade 2 LVEF shift (24.7% vs. 8.5%). Similar magnitude of change was seen in patients with or without baseline cardiac, LVD and hypertension risk factors.

Mean worst absolute change in LVEF from baseline was similar in the Combo 450 and vemurafenib arms (6.2% vs 4.3%). A higher percentage of patients in the Combo 450 arm than in the vemurafenib arm experienced a CTCAE Grade 0 to Grade 2 LVEF shift (28.4% vs 8.2%).

Ophthalmologic Evaluation

Changes in visual acuity (assessed by Snellen logMAR score) and intraocular pressure from baseline to end of treatment were similar between the Enco 300 P and Combo 450 RP populations. However, there was less of a shift towards reduced visual acuity in the Enco 300 P compared with the Combo 450 RP population (patients with a logMAR ≤0 with a shift to ≥0.3, 4.4% vs 10.1%, respectively).

There was less of a shift towards reduced visual acuity in the Enco 300 arm compared with the vemurafenib arm (patients with a logMAR ≤0 with a shift to ≥0.3, 4.6% vs 8.1%, respectively).

Safety in special populations

Elderly

In the Combo 450 RP population, 194 patients were <65 years and 80 patients were ≥65 years; 259 patients were <75 years and 15 patients were ≥75 years.

AEs (all grades) reported in more patients ≥65 years than patients <65 years included diarrhoea (43.8% vs 33%), increased GGT (21.3% vs 10.8%), pruritus (16.3% vs 6.2%) and increased blood ALP (15% vs 4.1%).

AEs (all grades) that were reported in at least 3 patients and in >25% more patients ≥ 75 years than patients < 75 years included nausea (66.7% vs. 37.8%), diarrhoea (60% vs. 34.7%) and asthenia (53.3% vs. 11.6%).

In the Enco 300 P population, 172 patients were <65 years and 45 patients were ≥ 65 years, 205 patients were < 75 years and 12 patients were ≥ 75 years.

AEs (all grades) reported in more patients ≥65 years than patients <65 years included asthenia (28.9% vs 16.9%), constipation (24.4% vs 14%) and increased GGT (22.2% vs 7.6%).

AEs (all grades) reported in at least 3 patients and in ≥ 25% more patients ≥ 75 years than patients < 75 years in the Enco 300 P population included, respectively: GGT increased (41.7% vs. 8.8%) and anaemia (33.3% vs. 5.4%).

A higher proportion of patients ≥65 years had Grade 3/4 AEs compared with those patients aged <65 years across all the study populations and all treatment arms in Study CMEK162B2301.

Table 72: 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 Hypotension[b]	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)
Fracture[c]	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)

Table 73: Overview of Safety according to age Enco 300P

		<65 years N=172 N (%)	65-74 years N=33 N (%)	75-84 years N=11 N (%)	≥85 years N=1 N (%)
At least one TEAEs	All grades	172 (100.0)	32 (97.0)	11 (100.0)	1 (100.0)
	Grade 3-4	114 (66.3)	23 (69.7)	9 (81.8)	1 (100.0)
At least one SAEs	All grades	55 (32.0)	11 (33.3)	5 (45.5)	0 (0.0)
	Grade 3-4	47 (27.3)	8 (24.2)	5 (45.5)	0 (0.0)
Fatal	All grades	10(5.8)	1(3.0)	1(9.1)	0 (0.0)
Hospitalization/prolong existing hospitalization	All grades	39(22.7)	10(30.3)	5(45.5)	0 (0.0)
Life-threatening	All grades	1(0.6)	1(3.0)	1(9.1)	0 (0.0)
Disability/incapacity	All grades	1(0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Other (medically significant)	All grades	9(5.2)	1(3.0)	1(9.1)	0 (0.0)
AEs leading to discontinuation	All grades	30 (17.4)	5 (15.2)	4 (36.4)	1 (100.0)
	Grade 3-4	21 (12.2)	4 (12.1)	3 (27.3)	1 (100.0)
SOC Psychiatric disorders	All grades	63 (36.6)	12 (36.4)	4 (36.4)	0 (0.0)
	Grade 3-4	7 (4.1)	1 (3.0)	0 (0.0)	0 (0.0)
SOC Nervous system	All grades	108 (62.8)	18 (54.5)	3 (27.3)	1 (100.0)
	Grade 3-4	18 (10.5)	4 (12.1)	0 (0.0)	0 (0.0)
Accidents and injuries SMQ	All grades	14 (8.1)	4 (12.1)	1 (9.1)	1 (100.0)
	Grade 3-4	2 (1.2)	1 (3.0)	0 (0.0)	0 (0.0)
SOC Cardiac disorders	All grades	24 (14.0)	4 (12.1)	3 (27.3)	0 (0.0)
	Grade 3-4	2 (1.2)	1 (3.0)	2 (18.2)	0 (0.0)
SOC Vascular disorders	All grades	30 (17.4)	10 (30.3)	3 (27.3)	1 (100.0)
	Grade 3-4	4 (2.3)	2 (6.1)	1 (9.1)	0 (0.0)
SMQ Cerebrovascular disorders[a]	All grades	5 (2.9)	3 (9.1)	0 (0.0)	0 (0.0)
	Grade 3-4	3 (1.7)	1 (3.0)	0 (0.0)	0 (0.0)
SOC Infections and infestations	All grades	79 (45.9)	12 (36.4)	3 (27.3)	1 (100.0)
	Grade 3-4	6 (3.5)	0 (0.0)	2 (18.2)	0 (0.0)
Sum of following PT	All grades	17 (9.9)	3 (9.1)	0 (0.0)	1 (100.0)
	Grade 3-4	3 (1.7)	2 (6.1)	0 (0.0)	0 (0.0)

Other subgroups

Regarding race, results should be interpreted with caution due to the relatively small number of patients in the Asian and Other (often <10) compared with the Caucasian subgroup.

No clinically relevant differences in the proportion of AEs were noted by gender or presence/ absence of baseline brain metastases, although the numbers with baseline brain metastases were low (8 in the Enco 300 P and 15 in the Combo 450 RP populations).

Hepatic Impairment

Study ARRAY-818-101 investigated the PK of encorafenib in subjects with mild hepatic impairment, as defined by Child-Pugh Score. Preliminary results indicate an approximate 25% increase in overall encorafenib exposure (AUCinf) compared to matching healthy subjects. Most AEs were mild or moderate, except for 1 Grade 3 AE of increased pancreatic enzymes deemed related and 1 Grade 3 AE of food allergy deemed not related.

Immunological events

Drug hypersensitivity is a known BRAFi class effect. Drug hypersensitivity (PTs of drug hypersensitivity, hypersensitivity, urticaria and angioedema) occurred in 2.9% of patients with no discontinuations, dose adjustments or study drug interruptions.

Drug hypersensitivity was recorded in 4.1% of the Enco 300 P population, with 0.5% Grade 3 events; 0.9% of patients discontinued and 1.8% patients required dose adjustment or study drug interruption.

In CMEK162B2301, the incidence of *drug hypersensitivity* was similar in the Combo 450 and vemurafenib arm (3.6% vs 4.8%) but the median time to first was longer in the Combo 450 arm (88.0 vs. 21.0 days).

Safety related to drug-drug interactions and other interactions

Study ARRAY-818-105 investigated the effects of posaconazole and diltiazem (strong and moderate CYP3A4 inhibitors, respectively) on the single-dose PK of encorafenib in healthy subjects. The higher encorafenib exposure resulted in more treatment emergent AEs. Concomitant administration of encorafenib with strong CYP3A4 inhibitors should be avoided due to increased encorafenib exposure and potential increase in toxicity.

For additional information, please refer to the Clinical Pharmacology section.

Discontinuation due to adverse events

About 10% of patients discontinued due to an AE in the Combo 450 RP population and 17.5% in the Enco 300 P population (Grade 3/4 AEs: 8.8% vs 13.4%). No AEs leading to study drug discontinuation were reported in ≥2% of patients in the Combo 450 RP population whilst PPE (3.7%) was the only AE in the Enco 300 P population.

In the Phase 3 study, AEs leading to study drug discontinuation in the Combo 450 arm included increased ALT and AST (2.6% each) whilst no specific AEs led to discontinuation in ≥2% of patients in either the Enco 300 or vemurafenib arms.

Table 74: 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)

	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 (%)	Vemurafeni N=186 n (%)
Any preferred term							
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

At the 4-month safety update, no AEs leading to study drug discontinuation were reported under new PTs in ≥2% of patients in any populations as compared to the initial MAA (except few switches to ~2% due to a single additional case in the population concerned).

Post marketing experience

The applicant did not submit post-marketing experience as the product has not yet been marketed.

2.6.1. Discussion on clinical safety

Safety information on encorafenib in combination with binimetinib in the proposed indication is based primarily on data from 274 patients in 3 clinical trials treated at the recommended dose of encorafenib 450 mg QD and binimetinib 45 mg BID [Combo 450 RP] in BRAF/ MEK inhibitor naïve patients. This is a small data set but considered sufficient to characterise the safety of the combination given that other BRAF/ MEK inhibitor combinations are already authorised. This data is supplemented by information from an additional 216 patients (total number 433 = Combo BP) treated with a combination of binimetinib 45 mg BID and encorafenib at doses from 300 mg to 600mg QD (Combo 400, n=4; Combo 600, n=62; Combo 450, n=367). In the Combo 450 subgroup, 274 patients were BRAF/MEK-treatment naïve (corresponding to the Combo 450 RP population) and 97 were non-naïve.

Safety data from 217 BRAF inhibitor naïve patients who received single agent encorafenib (Enco 300 P) population were provided for comparison. Data from the pivotal Study CMEK162B2301 were presented separately, for comparison of Combo 450, encorafenib and vemurafenib monotherapy (N=186).

The 4-month safety update provides an additional 750 patient-months of exposure in the Combo 450 RP population and 219 patient-months in the Enco 300 P population.

Safety data were also provided from 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). This was compared to the Combo 450 trial population.

The safety population is consistent with the target patient population with respect to gender and race, although the mean age of the trial patients was slightly lower than might be anticipated clinically; the results can be extrapolated to the intended population.

The median duration of exposure to study treatment was longer in the Combo 450 RP population than in the Enco 300 P population (50.6 weeks vs 29.7 weeks). The median relative dose intensity (RDI) was also higher for the combination (encorafenib 99.66%; binimetinib 99.5%) than single agent encorafenib (84.98%).

Despite the higher median relative dose intensity and longer median duration of exposure to study treatment in Combo 450 RP vs Enco 300 P, better general tolerability of Combo 450 (with encorafenib 450 mg QD) was observed compared to encorafenib single agent 300 mg QD or vemurafenib. A slightly lower percentage of patients in the Combo 450 RP, compared with the Enco 300 P population, experienced at least one Grade 3/4 AE (61.3% vs. 67.7%) or an AE leading to treatment discontinuation (11.7% vs. 18.0%). A bigger reduction was evident in AEs requiring dose interruption/change (52.2% vs. 71%). Similar percentages of patients experienced AEs requiring additional therapy (89.8% Combo 450 RP, 94.9% Enco 300 P).

The median time to onset of first Grade 3/4 AEs was longer in the Combo 450 RP population than in the Enco 300 P population: 2.6 months (95% CI: 1.8, 3.2) vs 0.4 months (95%CI: 0.3,0.9) [initial MAA].

Similarly, the proportion of patients experiencing these events was lower in the Combo 450 RP population than in the vemurafenib arm of Study CMEK162B2301.

However, the overall incidence of on-treatment deaths was higher in the Combo 450 RP than in Enco 300 P populations (10.2% vs 7.4%), with similar EAIRs of 0.73 vs 0.71 deaths per 100 patient-months respectively. Most on treatment deaths were due to malignant melanoma. Other causes of death in the Combo 450 RP population included multiple organ dysfunction, suicide, cerebral haemorrhage, euthanasia and myocardial infarction. In the Enco 300 P population, causes of death included pneumonia and acute MI. Mostly there was a single event involving a PT and no pattern was evident.

The proportion of patients with SAEs was higher in the Combo 450 RP population than in Enco 300 P (40.1% vs 32.7%) but similar after adjustment for treatment exposure (EAIRs of 3.9 and 3.5 per 100 patient-months); the EAIR was higher in the vemurafenib arm (4.96 per 100 patient-months). The only SAE which was increased by ≥2% in the Combo 450 RP vs Enco 300 P population was pyrexia (3.5% vs. 1.4%).

The overall safety profile of single agent encorafenib (Enco 300 P) was consistent with the mechanism of action and the known toxicities of BRAF inhibitors. The AE profile of the two BRAF inhibitors was similar but differences were evident. The overall EAIR was notably higher in the Enco 300 P population than in the vemurafenib arm (604.83 vs 226.32 per 100 patient-months). Vemurafenib caused relatively more photosensitivity, diarrhoea, pyrexia and squamous cell carcinoma whilst encorafenib (Enco 300 P) caused more constipation, neuropathy, facial paresis, myalgia and melanocytic naevus.

The most common ADRs (≥ 25 %) for Enco 300 P were hyperkeratosis (58.5%), alopecia (57.1%), palmar plantar erythrodysaesthesia syndrome (51.6%), rash (43.3%), arthralgia (43.3%), nausea (37.8%), dry skin (37.8%), myalgia (35.9%), headache (29%), fatigue (43.8%), vomiting (27.6%), pruritus (29.5%). The most common Grade 3/4 ADRs (≥ 5%) were PPE syndrome (12.4%), arthralgia (9.2%), myalgia (9.2%) and hyperkeratosis (6%). When adjusted for exposure, AEs with an EAIR of ≥5 per 100 patient-months in the Enco 300 P population included alopecia (13.14), PPE syndrome (10.45), arthralgia (8.4), hyperkeratosis (7.13) and nausea (5.87).

In the Combo 450 RP population, most of the observed toxicities were BRAF or MEK inhibitor driven and involved gastrointestinal, ocular, liver, muscular and cutaneous events. The most commonly reported adverse events (≥20%) in the Combo 450 RP population included fatigue (41.6%) and gastrointestinal disorders: nausea (41.6%), diarrhoea (38%), vomiting (28.1%), constipation (24.1%), arthralgia and increased blood CK (both 27.0%). Most of the events were Grade 1 or 2 in severity. The most common Grade 3/4 AEs were increased transaminases (5.5%), increased gamma GT (8.4%), hypertension (5.5%) and CK elevation (5.8%).

With combination treatment, the incidence of non-malignant skin AEs, arthralgia, myalgia, decreased appetite and insomnia was decreased compared to single agent encorafenib. The decreases in overall incidences of these AESIs with Combo 450 were generally associated with relevant decreases in Grade 3/4 events, dose adjustments/study drug interruptions and use of additional therapies. Conversely, the incidence of diarrhoea, abdominal pain, retinopathy, hypertension, increased blood CK and increased transaminases was greater with Combo 450 vs. Enco 300.

Adjusted for exposure, the only AE in the Combo 450 RP arm with an EAIR of ⩾5 per 100 patient-months was nausea (5.21). Adjusted for exposure, the rates of alopecia, PPE, arthralgia, hyperkeratosis and rash were higher with single agent encorafenib than combination treatment. Although no AEs with an EAIR of ⩾5 per 100 patient-months were reported at a higher incidence in the Combo 450 RP population than in the Enco 300 P population (difference of ⩾5) the rate of diarrhoea (4.87 vs. 1.46) and increased CK (2.66 vs. 0.1) was higher with combination treatment (Combo 450 RP vs Enco 300 P respectively). The increase in blood CK observed with Combo 450 was rarely associated with clinical symptoms.

The proportion of patients with haemorrhagic events was higher in the combination but the incidence was similar when adjusted for treatment duration (1.55 vs 1.52 cases per 100 patient months). No serious haemorrhage with established causal relationship to the combination was reported, although there were 3 cases of intracranial haemorrhage (1 fatal) in the setting of brain metastases. On review none of the hemorrhagic events correlated with changes in coagulation parameters (i.e. increased INR) or thrombocytopenia.

Haemorrhages, including major haemorrhagic events, can occur with encorafenib (see section 4.8). The risk of haemorrhage may be increased with concomitant use of anticoagulant and antiplatelet therapy. The occurrence of Grade ⩾3 haemorrhagic events should be managed with dose interruption or treatment discontinuation (see Table 3 in section 4.2) and as clinically indicated.

New primary malignancies, cutaneous and non-cutaneous, have been observed in patients treated with BRAF inhibitors and can occur when encorafenib is administered (see section 4.8). No case of new primary melanoma was reported in the Combo 450 RP population compared to 4.1% in the Enco 300 P population, and fewer patients experienced cutaneous squamous cell carcinoma in the Combo 450 RP compared to Enco 300 P single agent group (2.6% vs. 6.9%). Cutaneous malignancies such as cutaneous squamous cell carcinoma (cuSCC) including kerathoacanthoma has been observed in patients treated with BRAF-inhibitors including encorafenib.

New primary melanoma has been observed in patients treated with BRAF inhibitors including encorafenib (see section 4.8). For new primary cutaneous malignancies: No dose modifications are required for encorafenib. For new primary non-cutaneous RAS mutation-positive malignancies: it should be considered to discontinue encorafenib and binimetinib permanently.

Dermatologic evaluations should be performed prior to initiation of therapy with encorafenib in combination with binimetinib, 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. Encorafenib and binimetinib should be continued without any dose modification.

Based on its mechanism of action, encorafenib may promote malignancies associated with activation of RAS through mutation or other mechanisms. Patients receiving 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. It should be considered to permanently discontinue encorafenib in patients who develop RAS mutation-positive non-cutaneous malignancies. Benefits and risks should be carefully considered before administering encorafenib to patients with a prior or concurrent cancer associated with RAS mutation.

The most common binimetinib-driven ADRs included skin reactions, ocular reactions (retinal detachment, visual impairment), left ventricular dysfunction, hypertension and CK elevation. These can be managed via monitoring of left ventricular function, blood pressure and ophthalmological assessments with dose modifications as needed.

LVD defined as symptomatic or asymptomatic decreases in ejection fraction has been reported when encorafenib is used in combination with binimetinib.

It is recommended that left ventricular ejection fraction (LVEF) is assessed by echocardiogram or multi-gated acquisition (MUGA) scan before initiation of encorafenib and binimetinib, one month after initiation, and then at approximately 3-month intervals or more frequently as clinically indicated, while on treatment. If during treatment LVD occurs, see section 4.2 of binimetinib SmPC.

The safety of encorafenib in combination with binimetinib has not been established in patients with a baseline LVEF that is either below 50% or below the institutional lower limits of normal. Therefore, in these patients, binimetinib should be used with caution and for any symptomatic left ventricular dysfunction, Grade 3-4 LVEF or for absolute decrease of LVEF from baseline of ≥ 10%, binimetinib and encorafenib should be discontinued and LVEF should be evaluated every 2 weeks until recovery.

Ocular toxicities including uveitis, iritis and iridocyclitis can occur when encorafenib is administered. RPED has also been reported in patients treated with encorafenib in combination with binimetinib (see section 4.8).

Patients should be assessed at each visit for symptoms of new or worsening visual disturbance. If symptoms of new or worsening visual disturbances including diminished central vision, blurred vision or loss of vision are identified, a prompt ophthalmologic examination is recommended.
If, uveitis including iridocyclitis and iritis occurs during treatment, see section 4.2.

If during treatment patient develops RPED or RVO, see section 4.2 of binimetinib SmPC for guidance.

The incidence of liver function test abnormalities, including Grade 3/4 events, was higher with combination treatment compared to single agent encorafenib. However, none met the criteria for Hy's Law. There was one case of hepatic failure associated with disease progression that was not considered related to the combination treatment but attributed to new hepatic metastases. The incidence of GGT abnormalities was higher with combination treatment (14.6% overall; Grade 3/4 8.4%). This parameter is less specific for hepatic toxicity than ALT, ALP, bilirubin and other hepatic parameters and may not reflect hepatic toxicity. It may be due to the inducer effect of encorafenib on liver metabolism via CYP3A4.

Liver laboratory abnormalities including AST and ALT elevations have been observed with encorafenib (see section 4.8). Liver laboratory values should be monitored before initiation of encorafenib and binimetinib and monitored at least monthly during the 6 first months of treatment, then as clinically indicated. Liver laboratory abnormalities should be managed with dose interruption, reduction or treatment discontinuation (see section 4.2).

Renal dysfunction including creatinine elevation and renal failure (renal failure, acute kidney injury and renal impairment) was a common adverse effect for encorafenib as single agent and in combination with binimetinib in Combo 450. Renal dysfunction was frequently associated with gastrointestinal events/dehydration. Clinical data shows reversibility when it is managed through dose modification, standard care and corrective therapy.

Relatively few patients discontinued treatment due to an AE (11.7% vs. 18.0% - Combo 450 vs Enco 300).

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 proportions of patients experiencing adverse events (AE) and serious adverse events (SAE) were similar in patients aged <65 years and those aged ≥65 years. The most common AEs 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.

The incidence of pyrexia was distinctly lower in the Combo 450 RP population and secondary causes were generally evident. Pyrexia was the most commonly reported SAE by PT in the Combo 450 arm of Study CMEK162B2301 in 6 (3.1%) patients. None of the 6 patients had concurrent events of hypotension, chills/rigors, dehydration, renal failure or syncope and most had concurrent factors including disease progression or underlying infection which may have contributed to the pyrexia. Compared to other MEK/BRAF inhibitors, Grade 3/4 anaemia was reported more often with binimetinib/encorafenib. The incidence of abdominal pain was higher compared to other MEK/BRAF inhibitor combinations.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Encorafenib has minor influence on the ability to drive or use machines. Visual disturbances have been reported in some patients treated with encorafenib during clinical studies. Patients should be advised not to drive or use machines if they experience visual disturbances or any other adverse reactions that may affect their ability to drive and use machines (see sections 4.4 and 4.8).

Overdose Symptoms

At doses of encorafenib between 600 to 800 mg once daily, renal dysfunction (Grade 3 hypercreatinaemia) was observed in 3 out of 14 patients. The highest administered dose occurred as a dosing error in one patient who took encorafenib at a dose of 600 mg twice daily for 1 day (total dose 1200 mg). Adverse reactions reported by this patient were Grade 1 events of nausea, vomiting and blurred vision; all subsequently resolved.

Management

There is no specific treatment for overdose.

Since encorafenib is moderately bound to plasma proteins, haemodialysis is likely to be ineffective in the treatment of overdose with encorafenib. There is no known antidote for encorafenib. In the event of an overdose, encorafenib treatment should be interrupted and renal function must be monitored as well as adverse reactions. Symptomatic treatment and supportive care should be provided as needed.

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.

Dose modifications in case of adverse reactions are provided below and in Table 2 and 3 of the SmPC.

If treatment-related toxicities occur, then encorafenib and binimetinib should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose modifications are necessary for binimetinib only (adverse reactions primarily related to binimetinib) are: retinal pigment epithelial detachment (RPED), retinal vein occlusion (RVO), interstitial lung disease/pneumonitis, cardiac dysfunction, creatine phosphokinase (CK) elevation and rhabdomyolysis, and venous thromboembolism (VTE).

If one of these toxicities occurs, see section 4.2 of binimetinib SmPC for dose modification instructions for binimetinib.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

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 $\geqslant$ 48 weeks of study treatment.

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.

2.6.2. Conclusions on the clinical safety

Encorafenib was associated with more AEs than vemurafenib. The overall incidence was reduced by the combination with binimetinib, mainly due to the reduction in skin-related AEs. Diarrhoea, increased blood CK and liver function test abnormalities were more prevalent with the Combo 450 than single agent encorafenib 300mg. There was no difference in the exposure-adjusted incidence of SAEs between Combo 450 and encorafenib monotherapy. Most AEs appeared to be manageable with dose reduction/ interruption and additional therapy. Combo 450 led to an increased incidence of SAEs and Grade 3/4 AEs compared to Combo 300. The AE profile for Combo 300 should be conveyed in the SmPC, section 4.8 (**OC**).

2.7. Risk Management Plan

Safety concerns

Safety concerns for encorafenib	**Additional safety concerns for encorafenib in combination with binimetinib**
Important identified risks	
- Secondary skin neoplasms: cuSCC and new primary melanoma - Palmar-plantar erythrodysaesthesia syndrome	- Haemorrhage
Important potential risks	
- QT prolongation - Non-cutaneous malignancies with RAS mutation - Over-exposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors - Embryo-foetal toxicity - Over-exposure in patients with moderate to severe	- Hepatotoxicity

hepatic impairment - Potential for renal dysfunction due to overdose	
Missing information	
- Use in patients with severe renal impairment	None

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 encorafenib		
Secondary skin neoplasms: cutaneous squamous cell carcinoma and new primary melanoma	Routine: 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. Use restricted to physicians experienced in the treatment of cancer Additional: none	Routine Additional: none
Palmar-plantar erythrodysaesthesia syndrome	Routine: Dose modification recommendations in Section 4.2 of the SmPC Listed in Section 4.8 of the SmPC and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none	Routine Additional: none
Additional important identified risks for encorafenib in combination with binimetinib		
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. Use restricted to physicians experienced in the treatment of cancer.	Routine Additional: none

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional: none	
Important potential risks for encorafenib		
QT prolongation	Routine: Dose modification recommendations in section 4.2 of the SmPC Warning in Section 4.4 of the SmPC and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none	Routine Additional: none
Non-cutaneous malignancies with RAS mutation	Routine: Dose modification recommendations in section 4.2 of the SmPC Warning in Section 4.4 of the SmPC and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none	Routine Additional: none
Over-exposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors	Routine: Warning in section 4.4 of the SmPC and relevant PIL sections Discussion in section 4.5 Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none	Routine Additional: none
Embryo-foetal toxicity	Routine: Warning in Section 4.6 and information in Section 5.3 of the SmPC and relevant PIL section. Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer. Additional: none	Routine Additional: none
Over-exposure in patients with moderate to severe hepatic impairment	Routine: Dose modification recommendations in section 4.2 of the SmPC and PIL relevant section Warning in section 4.4 and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none	Routine Additional: none
Potential for renal dysfunction due to overdose	Routine:	Routine

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Listed in section 4.9 of SmPC Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none	Additional: none
Additional important potential risks for encorafenib in combination with binimetinib		
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. Use restricted to physicians experienced in the treatment of cancer. Additional: none	Routine Additional: none
Missing information for encorafenib		
Use in patients with severe renal impairment	Routine: Dosing recommendations in section 4.2 of the SmPC Warning in section 4.4 of the SmPC and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none	Routine Additional: none
Additional missing information for risks for encorafenib in combination with binimetinib		
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 0.5 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 encorafenib 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 encorafenib 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, Braftovi (encorafenib) 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 MAH applied for an indication of encorafenib in combination with binimetinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a 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), estimate the treatment effect of Combo 300 vs. vemurafenib in terms of PFS and OS and estimate the treatment effect of Combo 300 vs. Combo 450 in terms of PFS and OS.

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.

3.2. Favourable effects

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 results in the per protocol set (PPS) by BIRC were supportive of the primary analysis. 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).

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 disease control rate (DCR) per BIRC was 92.2% (95% CI 87.4, 95.6) in the Combo 450 arm compared with 84.0% (95% CI 78.1, 88.9) in the encorafenib arm and 81.7% (95% CI 75.4, 86.9) in the vemurafenib arm.

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).

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

For Combo 450 P, the incidence of AEs was 98.9% with Grade 3/4 AEs reported in 58.0% patients (Grade 4, 9.9%); the median time to onset of the first Grade 3/4 AE was 2.5 months. AEs led to dose interruption/ change in 47.1% patients, additional therapy in 86.1% and treatment discontinuation in 10.4%.

The safety of encorafenib (450 mg orally once daily) in combination with binimetinib (45 mg orally twice daily) was evaluated in 274 patients with BRAF V600 mutant unresectable or metastatic melanoma (hereafter referred to as the pooled Combo 450 population), based on two Phase II studies (CMEK162X2110 and CLGX818X2109) and one Phase III study (CMEK162B2301, Part 1). At the recommended dose (n = 274) in patients with unresectable or metastatic melanoma, the most common adverse reactions (≥25%) occurring in patients treated with encorafenib administered with binimetinib were fatigue, nausea, diarrhoea, vomiting, retinal detachment, abdominal pain, arthralgia, blood CK increased and myalgia.

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).

Encorafenib exposure and risk of toxicity is increased in patients with mild hepatic impairment and use of concomitant CYP3A4 inhibitors.

The addition of binimetinib (Combo 450 RP) attenuated some of the adverse events of special interest (AESIs) compared to single agent encorafenib (Enco 300 P). These were mainly non-malignant skin AESIs, myopathy -related AESIs (myalgia), cutaneous squamous cell carcinoma and new melanoma. Facial paresis (facial paralysis) was an AE associated with encorafenib monotherapy that was also reduced with combination treatment (7.4% vs. 0.7%), as was tachycardia (6% vs. 1.8%).

Other AESI were worsened or enhanced by the addition of binimetinib (Combo 450 RP compared to Enco 300 P). These included retinopathies (52.6% vs 12.4%); increased blood CK (24.8% vs 1.4%) with 5.5% Grade 3/4 events; left ventricular dysfunction (8.4% vs 1.8%); hypertension (12% vs 5.5%) with Grade 3/4 (6.2% vs 2.8%) and abnormal liver function tests (25.2% vs 13.8%). No cases consistent with Hy's Law were reported. There was one event of liver failure in the context of liver metastases, deemed unrelated to treatment.

The incidence of haemorrhage-related events was similar in the Combo 450 RP and Enco 300 P populations (15.7%-1.55 cases per 100 patient-months vs 12.9%-1.52 cases per 100 patient-months) Haemorrhage is a class effect for MEK inhibitors and is an important identified risk for binimetinib. Haemorrhagic events in the Combo 450 RP population (16.8%, 46/274) were mainly Grade 1/2 (14.2%) with few dose reductions or interruptions and treatment discontinuations in 3 (1.1%). The most frequent haemorrhagic events were GI. Intracranial haemorrhage was reported in 1.6% (3/192) of patients in the setting of new or progressive brain metastases including one fatal event.

The incidence of on-treatment deaths (within 30 days of the last dose) was similar for Combo 450 RP (8.4%), Enco300 P (6.9%) and vemurafenib (10.2%) and most of the deaths were due to malignant melanoma.

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 were no studies or data in patients with moderate or severe hepatic impairment and studies have shown that there is a risk for over-exposure in patients with moderate to severe hepatic impairment. Therefore, a warning in section 4.4 has been included that in the absence of clinical data, encorafenib is not recommended in patients with moderate or severe hepatic impairment.

Although a QT study has not been conducted, encorafenib was shown to have the potential to cause QT prolongation at clinically relevant doses. In Study CMEK162B2301, QTcF increases by >60 ms were observed in 5.4%, 3.9% and 5.6% of patients in the Combo 450, Enco 300 and vemurafenib arms, respectively and new QTcF values >500 ms were observed in 0.5%, 2.8% and 1.7% of patients, respectively. QTc prolongation is a class-effect of BRAF inhibitors. Therefore, a warning in the SmPC section 4.4 has been included.

Based on the mechanism of action, non-cutaneous malignancies could potentially arise as a result of treatment with encorafenib and binimetinib and therefore, a warning has been included in the SmPC section 4.4.

Encorafenib is mainly metabolised via CYP3A4 and there is a possibility of over-exposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors. A warning has been included in 4.4, with a description of concomitant administration of CYP3A4 inducers and inhibitors to avoid in section 4.5. Furthermore, a drug-drug cocktail interaction study will be submitted as a post-authorisation measure in order to better characterise the metabolic pathways and transporters involved in encorafenib elimination.

In non-clinical models, there is some evidence that there may be embryo-foetal toxicity associated with encorafenib administration. Therefore a warning has been included in section 4.6.

There are no data available in patients with severe renal impairment and PK population analysis has provided an indication that there is the potential for renal dysfunction due to overdose. Therefore, a warning has been included in section 4.4 that encorafenib should be used with caution in patients with severe renal impairment and that blood creatinine should be monitored as clinically indicated and managed with dose modification or discontinuation. In addition, 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 75: Effects Table for Encorafenib in Combination with Binimetinib for the Treatment of Adult Patients with Unresectable or Metastatic Melanoma with BRAF V600 mutation (data cut-off: 19 May 2016 – PFS Part 1; 9 Nov 2016- PFS Part 2; 7 Nov 2017 – OS

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Median PFS	Combo 450 vs Vem	mon	14.9	7.3	Strong; consistent across analyses + previous BRAF-MEKi combos	

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Median PFS	Enco 300 vs. Vem	mon	9.6	7.3	Strong; little uncertainty	
Median PFS	Combo 450 vs Enco 300	mon	14.9	9.6	Lacks statistical significance	
Median OS	Combo 450 vs Vem	mon	33.6	16.9	strong	
Median OS	Combo 450 vs Enco 300	mon	33.6	23.5		
Median PFS	Combo 300 vs Enco 300 (Part 2)	mon	12.9	7.4	Enco 300 PFS shorter than in Part 1	
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		

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
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.

The median PFS result for Combo 450 (14.9 months) compares very favourably with other BRAF-MEK inhibitor combinations already authorised (trametinib and dabrafenib, median PFS is 11.4 months or cobimetinib and vemurafenib with a median PFS of 12.3 months). The median potential durations of follow-up for OS were 37.2 months (Combo 450) and 35.9 months (vemurafenib) in Study CMEK162B2301 (using Kaplan Meier Approach), 22.3 months (vemurafenib/cobimetinib) and 17.4 months (vemurafenib) in coBRIM, and 26.1 months (dabrafenib/trametinib) and 17.8 months (vemurafenib) in COMBI-v. The median OS of 33.6 months with Combo 450 is impressive in comparison with the other regimens (median OS 22.3 to 26.1 months).

The ORR and the disease control rate were high for Combo 450 and the onset of response was rapid, within around 2 months, in responders. This corresponds to the first clinical visit and it is possible that responses occurred earlier, allowing relief of symptoms, particularly for patients with bulky disease.

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 encorafenib against BRAF V600E/K/R, the indication has been expanded to include all BRAF V600 mutations as it is expected that encorafenib may target and inhibit BRAF regardless of the type of 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 Braftovi 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 decision that the benefit-risk balance of Braftovi is favourable in the following indication:

Encorafenib in combination with binimetinib 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 encorafenib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.