25 July 2024
EMA/CHMP/372317/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mektovi	Binimetinib
Braftovi	Encorafenib

Procedure No. EMEA/H/C/xxxx/WS/2538

Note

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

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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AJCC	American Joint Committee on Cancer
ALT	Alanine Transaminase
ATP	Adenosine Tri-Phosphate
AUC	Area Under the Concentration-Time Curve
BA	Bioavailability
BID	Twice Daily
BRAF	B-Raf Proto-Oncogene, Serine/Threonine Kinase
BRAF	Serine/Threonine-Protein Kinase B-Raf
CDER	Centre for Drug Evaluation and Research
CDK	Cyclin Dependent Kinase
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
CO	Clinical Overview
COD	Cut-off Date
Combo 450	Encorafenib 450 mg QD in combination with binimetinib 45 mg BID
CR	Complete Response
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
ctDNA	circulating tumour DNA
cuSCC	Cutaneous Squamous Cell Carcinoma
D	Day
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DFS	Disease Free Survival
DLT(s)	Dose Limiting Toxicity(ies)
DLP	Data Lock Point
DMC	Data Monitoring Committee
DOR	Duration of Response
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group-Performance
Status	
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
Enco 300	Encorafenib 300 mg
EOT	End of Treatment
ERK	Extracellular Signal-Regulated Kinase
ESMO	European Society for Medical Oncology
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND(s)	Investigational New Drug(s)
ISP	Integrated safey population
IRR	Independent Radiology Review
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

Max	Maximum
MEB	Medicines Evaluation Board
MEK	Mitogen-Activated Protein Kinase Kinase
Min	Minimum
MPA	Medical Products Agency
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCA	Non-Compartmental Analysis
NCCN	National Comprehensive Cancer Network
NE	Not Estimable
NRAS	Neuroblastoma RAS Viral Oncogene Homologue Not Specified
ORR	Objective Response Rate
OS	Overall Survival
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PDL-1	Programmed Death (Receptor) Ligand 1
pERK	Phosphorylated Extracellular Signal-Regulated Kinase
PFS	Progression-Free Survival
P-gp	P-glycoprotein
PI3K	Phosphoinositide 3-Kinase
PK(s)	Pharmacokinetic(s)
PopPK	Population PK
PPE	Palmar-Plantar Erythrodysaesthesia
PPS	Per-Protocol Set
PR	Partial Response
PS	Performance Status
QD	Once Daily
RAF	Serine/Threonine-Protein Kinase
RAS	Rat Sarcoma Viral Oncogene Homologue
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	Recommended Phase 2
Dose	
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SC	Steering Committee
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Standard Deviation
Tmax	Time to Maximum Observed Plasma Concentration
TTR	Time to Response
ULN	Upper Limit of Normal
US	United States (of America)
vs.	Versus
Vz/F	Volume of Distribution

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pierre Fabre Medicament submitted to the European Medicines Agency on 9 October 2023 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include binimetinib in combination with encorafenib for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation for MEKTOVI and BRAFTOVI based on results from study PHAROS (Study ARRAY-818-202) at the primary completion date; this is a Phase II, open-label, multicentre, non-comparative study (interventional). As a consequence, sections 4.1, 4.4, 4.8, 5.1, 5.2, 9 and 10 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection for MEKTOVI.

The worksharing procedure requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0351/2023 for encorafenib (Braftovi) and P/0349/2023, for binimetinib (Mektovi) on the granting of a (product-specific) waiver.

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 WSA 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.

WSA request for additional market protection

Initially, the WSA requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication for MEKTOVI (binimetinib). The request was withdrawn during the procedure.

Scientific advice

The WSA did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Appointed Rapporteur for the WS procedure:

Janet Koenig

Timetable	Actual dates
Submission date	9 October 2023
Start of procedure:	28 October 2023
CHMP Rapporteur's preliminary assessment report circulated on:	19 December 2023
PRAC Rapporteur's preliminary assessment report circulated on:	3 January 2024
PRAC members comments	4 January 2024
Updated PRAC Rapporteur report circulated on:	5 January 2024
PRAC RMP advice and assessment overview adopted by PRAC	11 January 2024
CHMP members comments	15 January 2024
Joint Rapporteur's updated assessment report circulated on:	19 January 2024
Request for supplementary information adopted by the CHMP on:	25 January 2024
Rapporteur's preliminary assessment report on the WSA's responses circulated on:	26 April 2024
PRAC Rapporteur Assessment Report	3 May 2024
PRAC members comments	7 May 2024
Updated PRAC Rapporteur Assessment Report	8 May 2024
PRAC Outcome	16 May 2024
CHMP members comments	17 May 2024
Joint Rapporteur's updated assessment report on the WSA's responses circulated on:	23 May 2024
Request for supplementary information (RSI)	30 May 2024
PRAC Rapporteur Assessment Report	1 July 2024
PRAC members comments	3 July 2024
CHMP Rapporteur Assessment Report	10 July 2024
PRAC Outcome	11 July 2024
CHMP members comments	15 July 2024
Updated CHMP Rapporteur Assessment Report	18 July 2024
CHMP Opinion	25 July 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

State the claimed therapeutic indication

Non-small cell lung cancer (NSCLC)

Encorafenib in combination with binimetinib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation (see sections 4.4 and 5.1).

Non-small cell lung cancer (NSCLC)

Binimetinib in combination with encorafenib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation (see sections 4.4 and 5.1).

Epidemiology and risk factors, screening tools/prevention

Globally, lung cancer is the most commonly occurring cancer in men and the third most commonly occurring cancer in women. Worldwide, as of 2020, the incidence of lung cancer was about 2.2 million cases, resulting in 1.80 million (18.0%) deaths yearly (GLOBOCAN, 2020). Lung cancer is the second most common cancer in Europe with an incidence of about 477,500 cases corresponding to 11.8% of the new cancer diagnoses (excluding non-melanoma skin cancers) and it is the leading cause of cancer deaths with more than 380,000 deaths corresponding to about 20% of the cancer deaths in Europe (Dyba, 2021). Mainland Europe exhibits wide geographic variations in lung cancer incidence with highest rates observed in central and Eastern Europe. Socioeconomic and educational inequalities, as well as diagnosis at later stages of disease, contribute to variability in lung cancer incidence and mortality (Barta, 2019).

NSCLC is the most common subtype of lung cancer, accounting for approximately 85% of all lung cancer diagnoses and it comprises three main histological subtypes. Adenocarcinoma is the most common, accounting for around 60% of all NSCLC cases, followed by squamous cell carcinoma (around 25% of all NSCLC cases) and large cell carcinoma (around 10%).). Most newly diagnosed NSCLC patients have advanced disease; in industrialised countries including Eurozone, proportion of Stage IV disease at diagnosis is commonly between 45% and 55% and stage III are reporting in 20% to 30% of patients (Walters, 2013; Sant, 2023).

NSCLC is a heterogeneous disease comprised of an expanding number of biologically distinct and clinically relevant molecular subsets. Approximately 2% to 4% of patients with NSCLC have mutations in the BRAF gene (Hendriks, 2023a - supplementary text) with half of these driven by the BRAF V600E mutation (Class 1) and the other half driven by non-V600E mutations distributed throughout exons 11 and 15 collectively (Class 2 and 3) (Kris, 2014; Zheng, 2015).

In a cohort of 23,396 consecutive patients with lung cancer who underwent comprehensive genomic profiling (CGP) during clinical care, 5.5% of adenocarcinomas and 1% of squamous and small-cell tumours harboured BRAF alterations (Sheikine, 2018). Among all lung adenocarcinomas and NSCLC NOS, 40% and 29% of BRAF alterations, respectively, were *BRAF* V600E.

Biologic features, Aetiology and pathogenesis

There are conflicting reports regarding a specific gender association of BRAF mutations, however BRAF-V600E is consistently reported as being more frequent in female than male patients (Cui, 2017; Chen, 2014).

The literature is divided as to an association with smoking status: whilst most studies conclude that BRAF mutations are commonly associated with a current or former status (Yeh, 2013; Sasaki, 2012; O'Leary, 2019), several reports or reviews note that V600E mutation occurs most frequently in never smoker (Marchetti, 2011; Cui, 2017), whilst others find the opposite or an absence of correlation (Kinno, 2014; Cardarella, 2013; Brustugun, 2014; Villaruz, 2015).

Histologically, BRAF V600E-mutated adenocarcinomas are mucinous with a micropapillary growth pattern and intense thyroid transcription factor-1 (TTF-1) expression (Bustamante Alvarez, 2019) that is associated with shorter progression-free survival and overall survival in univariate analysis (hazard ratio [HR] 2.67; $p<0.001$ and HR 2.97; $p<0.001$, respectively) and multivariate analysis (HR, 2.19; $p<0.011$ and HR, 2.18; $p<0.14$, respectively). BRAF non-V600E tumours were found to have micropapillary histology in only 12% of the cases.

BRAF V600E mutations are mostly mutually exclusive with most druggable abnormalities present in NSCLC (Planchard, 2018; Li, 2014).

Clinical presentation, diagnosis and stage/prognosis

More than half of people newly diagnosed with lung cancer can be expected to die within 1 year of diagnosis (Howlader, 2020). Based on a US large database, the 5-year relative survival rate from 2012 to 2018 for participants with lung cancer was 23%. The 5-year relative survival rate varies markedly for participants diagnosed at local stage (61%), regional stage (34%), or distant stage (7%) [American Cancer Society, 2023]. The 5- year survival rate for participants diagnosed with Stage IVM1a lung cancer is approximately 10% and it is <1% for Stages IVM1b and c. Major advancements in the treatment of metastatic NSCLC associated with the development of targeted therapy and immunotherapy has led to improved survival rates in participants with advanced or metastatic disease benefiting from these therapies(Hendriks, 2023; Chen, 2020; Brahmer, 2022; De Castro, 2022, Johnson, 2022).

Retrospective analyses exploring the activity of chemotherapy in participants with advanced NSCLC have revealed that advanced NSCLC participants harbouring BRAF V600 mutations present poor prognosis when administered with chemotherapy (Barlesi, 2016; O'Leary, 2019). In addition, participants with BRAF V600E mutations appear to show inferior responses to platinum-based chemotherapy when compared to BRAF non-V600E-mutated participants or wild-type participants (Ding, 2017, Cardarella, 2013, Marchetti, 2011). However, several reports showed that NSCLC participants harbouring BRAF V600E mutations seemed to have extended survival compared with participants without oncogenic drivers or that BRAF mutation was not prognostic of overall survival (Tissot, 2016; Couraud, 2019). Because of limited number of patients with BRAF V600 mutations included in these studies, their results should be interpreted with caution.

Management

Whilst studies on the use of immune checkpoint inhibitors (ICIs) with a longer follow-up have set immunotherapy as the new standard of care for the first-line treatment of advanced or recurrent disease in non-oncogene-addicted patients, (Brahmer, 2022; De Castro, 2022; Johnson, 2022), there are limited data on the benefit of ICI in the BRAF-mutated population (Hendriks, 2023a). Retrospective

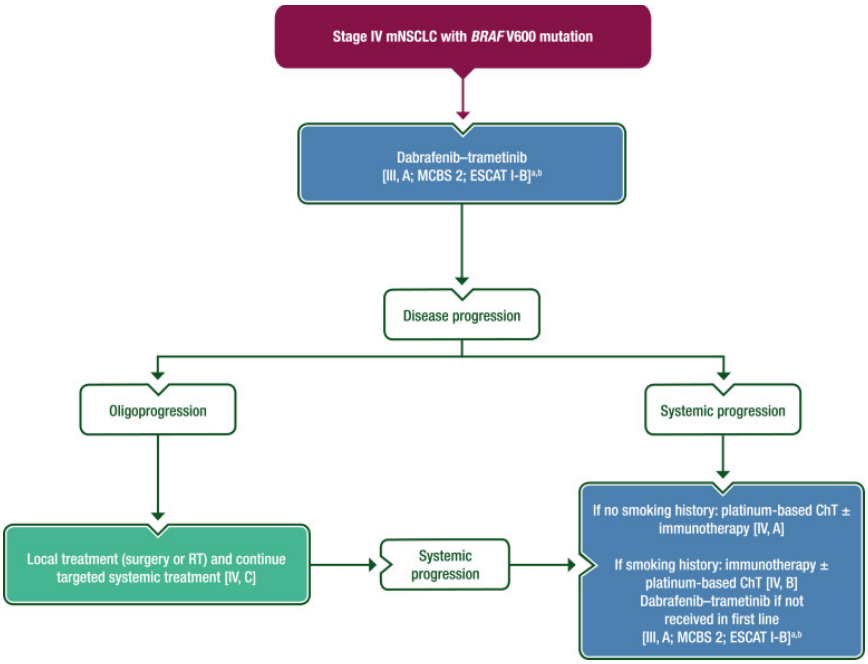
analyses in small series have indicated limited efficacy of ICIs in BRAF-mutant NSCLC (Tabbò, 2022). Results of the international IMMUNOTARGET study (43 participants with BRAF-mutated, 40% V600E) showed poor outcomes in BRAF-mutated participants, with an ORR of 24% and a mPFS of 3.1 months (Mazieres, 2019). Consistent with this, another retrospective study investigating the efficacy of single-agent ICI in oncogene-addicted metastatic NSCLC, confirmed that patients with BRAF V600-mutated tumours (n = 26 participants, mostly patients with ≥2 prior lines of therapy) showed an ORR of 26% and a mPFS of 5.3 months (Guisier, 2020).

Phase II trials have demonstrated the efficacy of BRAF and MEK inhibitors, for patients harbouring V600 mutation. In a vemurafenib basket trial including BRAF V600-mutated NSCLC (n = 62), ORR was 38% in previously untreated participants and 37% in previously treated participants (Hyman, 2015; Subbiah, 2019). In a separate study of 101 BRAF V600-mutant patients (of them 97 patients were BRAF V600E mutant) that included 49.5% previously untreated participants, ORR was 45%, mDoR 6.4 months, mPFS 5.2 months and mOS 10.0 months (Mazieres, 2020). A prospective Phase II study (BRF113928) of dabrafenib monotherapy (n = 78), or combination therapy with a MEK inhibitor (trametinib) beyond first-line (n = 57) or in first-line (n = 36) in patients with BRAF V600E-mutated metastatic NSCLC reported an ORR of 33% with mPFS and mDoR of 5.5 and 9.6 months, respectively with dabrafenib monotherapy (Planchard, 2016b). With the combination of dabrafenib–trametinib in pre-treated participants, the ORR was 68% (54.8-80.1) and mPFS and mDoR were 10.2 months (95% CI 6.9-16.7 months) and 9.8 months (95% CI 6.9-18.3 months), respectively (Planchard, 2021). With combination dabrafenib–trametinib therapy in treatment-naïve participants, the ORR was 64% (46%-79%) and mPFS and mDoR were 10.8 months (95% CI 7.0-14.5 months) and 10.2 months (95% CI 8.3-15.2 months), respectively. In pre-treated and treatment-naïve participants, respectively, who received the combination treatment, the mOS was 18.2 months (95% CI 14.3-28.6 months; 4- and 5-year survival rates: 34% and 22%, respectively) and 17.3 months (95% CI 12.3-40.2 months; 4- and 5-year survival rates: 26% and 19%, respectively) (Planchard, 2021).

Based upon the improved outcomes associated with targeted therapies in patients with metastatic NSCLC, molecular characterisation of NSCLC tumours has become a key tool for facilitating treatment decisions and the clinical management of patients with NSCLC (Hendriks, 2023a). The ESMO 2023 guidelines for the management of oncogene -addicted metastatic NSCLC (mNSCLC) confirm mutation testing as a mandatory step in disease management and extend the list of oncogenic drivers that should be tested for (including MET, RET, NTKR) (Hendriks, 2023a).

According to the European Society For Medical Oncology (ESMO) and National Comprehensive Cancer Network® (NCCN®) treatment guidelines 2023, the preferred first-line treatment for BRAF V600 (ESMO) / V600E (NCCN) mutated metastatic NSCLC in adults is dabrafenib and trametinib (Figure 1). Single agent vemurafenib or dabrafenib are treatment options if the preferred combination is not tolerated. If participants progress on these targeted treatments, then systemic therapy (chemotherapy and/or immunotherapy) should be offered, and the type of therapy will vary depending on tumour histology type (ADC or SCC). [Hendriks, 2023a; Planchard, 2018; NCCN 2022].

Figure 1: treatment algorithm for patients with BRAF V600 mutations. (Hendriks 2023a)



Systemic therapy regimen recommendations for non-oncogene-addicted mNSCLC are outlined in a separate guideline (Hendriks, 2023b).

Advanced BRAF V600-mutated NSCLC is an aggressive disease with a poor prognosis. According to ESMO guidelines for oncogene-addicted NSCLC, the preferred first-line treatment for adults with BRAF V600 mutated metastatic NSCLC is dabrafenib and trametinib. Currently only this combination is approved. In order to expand the therapeutic options for patients with NSCLC with BRAF V600 mutation, there is an intent to develop new effective and better tolerated treatment regimens. Due to the specific adverse reaction profiles of BRAF and MEK inhibitor combinations, specific combinations may be more suitable than others in certain patients (Garutti, 2022).

2.1.2. About the WS products

Binimetinib (Mektovi) is an adenosine triphosphate (ATP)-uncompetitive, reversible inhibitor of the kinase activity of mitogen-activated extracellular signal-regulated kinase kinases 1/2 (MEK1 and MEK2).

Encorafenib (Braftovi) is a highly selective ATP-competitive small- molecule RAF kinase inhibitor acting on the RAS/RAF/MEK/ERK pathway in tumour cells expressing BRAF V600 mutations, including NSCLC cell lines.

Encorafenib and binimetinib received first regulatory approval on 27 June 2018 in the US and on 20 September 2018 in the EU (centralised procedure). The first marketing authorisation was granted for encorafenib to be used in combination with binimetinib (and vice versa) for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Further marketing approvals were granted later in other countries in the same indication. These approvals were based on results from the Phase 3 Study CMEK162B2301.

A variation of the indication was granted for encorafenib to be used in combination with cetuximab for the treatment of adult patients with BRAF V600E mutant metastatic colorectal cancer (mCRC) who

have received prior systemic treatment in the EU (centralised procedure, 2 June 2020) and in several countries such as the US (8 April 2020), Further marketing approvals were granted later in other countries in the same indication. These approvals were based on results from the Phase 3 study ARRAY 818-302. The variation of the indication did not comprise Mektovi (binimetinib) in the mentioned mCRC indication.

Based on the results of the Phase 2 study (PHAROS), marketing authorisation application for Braftovi in combination with Mektovi (binimetinib) has been submitted in the US, for the treatment of adult participants with metastatic non-small-cell lung cancer (NSCLC) with a BRAF V600 mutation, as detected by an FDA-approved test. This application was granted by the FDA on Oct 11, 2023.

Based on these study results of this SAT (PHAROS), the Applicant, Pierre Fabre Medicament, is applying for the following indication (for the combination of the two products):

Treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation (see sections 4.4 and 5.1).

The final agreed indication is:

Treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600E mutation

Binimetinib is supplied as 15 mg film-coated tablets for oral administration. The proposed recommended dose in this new indication is 45 mg twice daily (BID).

The line extension procedure for Mektovi EMEA/H/C/004579/X/0029 led to the authorisation on 18 June 2024 of a new single 45 mg binimetinib film coated tablet.

Encorafenib is supplied as 50 mg and 75 mg hard capsules for oral administration. The proposed recommended dose in this new indication is 450 mg once daily (QD).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

No CHMP scientific advice was given for the new indication.

The MAH/applicant requested (date 28 April 2023) a pre-submission meeting to which written responses were provided on 15 May 2023 (see module 1.2). Main issue, besides formal aspects of a WSP, was pooling of the overall safety database with the safety data of new PHAROS study in BRAF mutated NSCLC patients.

For justifying the primary endpoint ORR of the (uncontrolled) SAT PHAROS, the MAH/applicant refers to the EMA/CHMP anticancer guidance on the evaluation of anticancer medicinal product in man (EMA/CHMP/205/95 Rev.6) with a specific mention of the "relevant" appendix 1: "In single arm studies, ORR in the per-protocol analysis set may be reported as primary outcome measure. External independent review of tumour response is encouraged, according to the objectives of the trial."

2.1.4. General comments on compliance with GCP

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

2.2. Non-clinical aspects

2.2.1. Introduction

Binimetinib is an ATP-uncompetitive, reversible inhibitor of the kinase activity of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. Binimetinib inhibits activation of MEK by BRAF and inhibits MEK kinase activity.

Encorafenib is a potent and highly selective ATP-competitive small molecule RAF kinase inhibitor.

Binimetinib and encorafenib both inhibit the MAPK pathway resulting in higher anti-tumour activity. Additionally, the combination of encorafenib and binimetinib prevented the emergence of treatment resistance in BRAF V600E mutant human melanoma xenografts in vivo.

For the proposed new additional indication, the MAH provided data from a BRAFV600E NSCLC xenograft model, in which the combination of binimetinib (3.5 mg/kg BID) and encorafenib (20 mg/kg QD) has been tested for its anti-tumour activity.

2.2.2. Pharmacology

Binimetinib is an ATP-uncompetitive, reversible inhibitor of the kinase activity of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. In a cell- free system, binimetinib inhibits MEK1 and MEK2 with the half maximal inhibitory concentration (IC50)'s in the range 12-46 nM. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. In melanoma and other cancers, this pathway is often activated by mutated forms of BRAF, which activates MEK. Binimetinib inhibits activation of MEK by BRAF and inhibits MEK kinase activity. Binimetinib inhibits growth of BRAF V600 mutant melanoma cell lines and demonstrates anti-tumour effects in BRAF V600 mutant melanoma animal models.

Combination with encorafenib

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

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

To confirm the efficacy of the combination of binimetinib and encorafenib in the new proposed indication in NSCLC, results from an appropriate study were provided (study BEL0331B).

Study BEL0331B

The objective of this study was to determine the efficacy of binimetinib and encorafenib in the DFCI-306, EGFR del19/T790M; BRAF V600E model.

Study Design:

Study Groups					
Group #	Test Agent	Dose	Dosing Volume	Dosing Schedule	Number of Animals
1	Vehicle control	-	5 mL/kg	PO, qd x 26 days	8
2	Encorafenib	20 mg/kg	5 mL/kg	PO, qd x 26 days	8
3	Binimetinib	3.5 mg/kg	5 mL/kg	PO, bid x 26 days	8
4	Encorafenib + Binimetinib	20 mg/kg + 3.5 mg/kg	5 mL/kg + 5 mL/kg	PO, qd x 26 days + PO, bid x 26 days	8

50 female NSG mice, 9-weeks of age were implanted with DFCI-306 tumour fragments dipped in Matrigel subcutaneously in the right flank.

When tumour volumes reached 101 – 240 mm^3 (180.25 ± 44.34; mean ± SD), mice were randomly assigned to treatment groups #1-4 as indicated in the table above, and treatment was initiated next day (day 1). Tumour volumes were determined twice a week using calliper measurements, and body weights were obtained twice weekly.

On day 13, 2 mice in the combination group (#309 and #398) were given a drug holiday due to >15% body weight loss. The dosing continued from day 14 as the body weights recovered.

In the encorafenib group, animals in one cage (animal #s 305, 315, 338 and 345) lost >15% body weight on day 41 due to water valve not operating properly. They recovered quickly once they were given bottled water and supplemental fluids.

Mice were euthanized when tumour ulceration was observed or when tumour volume exceeded 2000 mm^3.

The study was terminated on day 94.

Results:

Figure 2: Tumour volume plot from study BEL0331B (Mean ± SE)

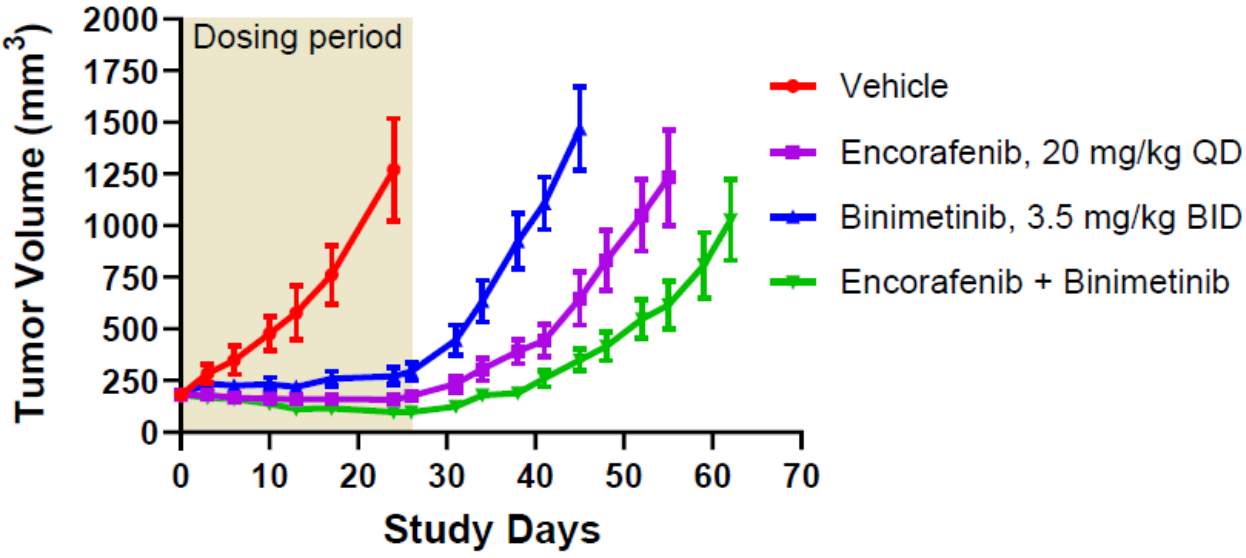


Table 1: Efficacy summary in the DFCI-306 model from study BEL0331B

Compound	Dose	% TGI (Day 24)	% Reg	Days to 400% Target Tumor Volume	T - C (Days)
Vehicle	-	-	-	16.2	-
Encorafenib	20 mg/kg qd x 26	100	13	47.1	30.9
Binimetinib	3.5 mg/kg bid x 26	91.7	0	36.2	20
Encorafenib + Binimetinib	20 mg/kg qd x 26 + 3.5 mg/kg bid x 26	100	45.7	56	39.8

% TGI (Tumor Growth Inhibition): Calculated using the formulae: [-100 x ((V_T day X - V_T day 0) / (V_C day X - V_C day 0))] + 100, where V_T is the mean tumor volume of treated group on days 0 or X and V_C is the mean tumor volume of control group on days 0 or X.

% Reg: Maximum % regression. % Regression was calculated as follows: [100-((V day X/ V day 0)*100)), where V is mean tumor on days 0 or X.

T - C: Growth delay calculated as T - C, where T and C are times in days for mean tumor size in the treated (T) and control (C) groups to reach 400% of the initial tumor volume.

2.2.3. Pharmacokinetics

At the time of the initial marketing authorisation application, pharmacokinetics data were generated in vivo in multiple preclinical species (mouse, rat, dog and monkey), and in vitro data in multiple species including human. A comprehensive work has been carried out to identify encorafenib and binimetinib metabolites in several species, including a mass-balance study in the intact and bile-duct cannulated rat and the monkey, in addition to a whole-body autoradiography study in the rat. The results are supportive of selecting the rat and the monkey for the toxicology studies in these species.

No preclinical pharmacokinetic studies were performed with encorafenib and binimetinib in combination.

No new preclinical pharmacokinetics studies were conducted in the context of the current application.

2.2.4. Toxicology

Repeated oral administration of binimetinib in rats for up to 6 months was associated with soft tissue mineralisation, gastric mucosal lesions and reversible minimal to mild clinical pathology changes at 7 to 12.5 times human therapeutic exposures. In a gastric irritation study in rats, an increased incidence of superficial mucosal lesions and of haemorrhagic ulcers were observed. In cynomolgus monkeys, oral administration of binimetinib was associated with gastro-intestinal intolerance, moderate clinical pathology changes, bone marrow hypercellularity and microscopic findings of gastrointestinal inflammation, reversible at the lowest doses which were below human therapeutic exposures.

Carcinogenic potential of binimetinib was not evaluated. Standard genotoxicity studies with binimetinib were negative.

The potential embryo-foetal effects of binimetinib were evaluated in rats and rabbits. In rats, lower gestational body weight gain and foetal body weights and a decreased number of ossified foetal

sternebrae were noted. No effects were noted seen at 14-times the human therapeutic exposures. In rabbits, mortality, maternal physical signs of toxicity, lower gestational body weight and abortion were observed. The number of viable foetuses and foetal body weights were reduced and post-implantation loss and resorptions were increased. An increased litter incidence of foetal ventricular septal defects and pulmonary trunk alterations was noted at the highest doses. No effects were observed at 3times the human therapeutic exposure.

Fertility studies were not conducted with binimetinib. In repeat-dose toxicity studies, no concern in terms of fertility was raised from pathological examination of reproductive organs in rats and monkeys.

Binimetinib has phototoxic potential in vitro.

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

2.2.5. Ecotoxicity/environmental risk assessment

Updated ERAs have been provided for Braftovi (API Encorafenib) and Mektovi (API Binimetinib) to consider a worksharing/extension of indication to extend the indication of the combination binimetinib/encorafenib for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation.

The updated ERAs are based on the ERAs of the initial marketing authorisations Braftovi EMEA/H/C/4580 and Mektovi EMEA/H/C/4052, which at that time had been considered complete and acceptable.

Table 2: Braftovi (active substance Encorafenib) – PEC/PNEC assessments

	PEC (µg/L)	PNEC (µg/L)	PEC/PNEC
Microorganisms	0.0559	100000	5.59 × 10-7
Surface water	0.0559	21	2.7 × 10-3
Groundwater	0.014	21	6.7 × 10-4
	PEC (µg/kg dwt)	PNEC (µg/kg dwt)	PEC/PNEC
Sediment	13.6	5580	2.4 × 10-3

Table 3: Mektovi (active substance Binimetinib) – PEC/PNEC assessments

	PEC (µg/L)	PNEC (µg/L)	PEC/PNEC
Microorganisms	0.006	100000	6.03 × 10-8
Surface water	0.006	65	9.3 × 10-5
Groundwater	0.0015	65	2.3 × 10-5
	PEC (µg/kg dwt)	PNEC (µg/kg dwt)	PEC/PNEC
Sediment	0.913	1000	9.1 × 10-4

2.2.6. Discussion on non-clinical aspects

The MAH provided data from a NSCLC xenograft model, in which binimetinib, encorafenib and the combination of both were tested.

The combination of binimetinib and encorafenib resulted in tumour growth inhibition in the DFCI-306 model with 45.7% tumour regression and a tumour growth delay of about 40 days. Encorafenib alone inhibited tumour growth in 4 out of 8 of animals (50%) at the end of the 26-day treatment period whereas the combination with binimetinib resulted in tumour regressions in all 8 animals (100%) compared with no regressions in the binimetinib only treatment group.

Thus, the combination of binimetinib and encorafenib in the DFCI-306 BRAFV600E NSCLC xenograft model showed higher activity compared to binimetinib or encorafenib alone.

Environment Risk Assessment

No new experimental studies were provided for the present worksharing application but new PECsurfacewater values were calculated to be 0.0559 µg/l for Braftovi and 0.00603 µg/l for Mektovi, respectively. Updated PEC/PNEC calculations showed that a risk to the aquatic and sediment compartment is not indicated. Assessments of the risk to the terrestrial compartment are considered not necessary.

However, both active substances have to be classified as very persistent (vP) in water/sediment systems as encorafenib showed a half-life (DT50) of 1000 days in sediment at 20 °C and DT50 of 203.7 - 468.6 days in the total system at 20 °C. Further, a transformation product of binimetinib formed in water – sediment systems shows a half-life (DT50) of 295 d (normalized to 12°C as average temperature in the EU).

2.2.7. Conclusion on the non-clinical aspects

The non-clinical data submitted are considered acceptable.

Based on the data submitted in this application, the new indication does not lead to a significant increase in environmental exposure further to the use of binimetinib nor encorafenib.

Considering the above data, Braftovi and Mektovi should be used according to the precautions stated in the SmPC to minimise any potential risks to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The WSA 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

Tabular Overview of the Clinical Study and Population PK and Exposure-Response Analyses of Encorafenib and Binimetinib Combination Pharmacokinetics to Support the NSCLC indication

Study Code	Short Title	Design Number of subjects (n)	Formulation	PK sampling[1]
PHAROS (C4221008)	A Phase 2 open-label, multicentre, single-arm study to determine the safety, tolerability and efficacy of the combination of encorafenib + binimetinib in participants with *BRAF* V600-mutant metastatic NSCLC	Open label, multiple dose Treatment-naïve: 59 Previously treated: 39 Total: 98	Capsule (encorafenib)	Serial and sparse
			Clinical studies included in dataset	
PMAR-EQDD-C422a-sNDA-1467 and erratum	Population Pharmacokinetic Modeling of Encorafenib in Participants with BRAF V600-mutant NSCLC in PHAROS	Treatment-Naive 59 Previously Treated 37	PHAROS (C4221008)	
PMAR-EQDD-C422a-sNDA-1468, erratum and erratum2	Population Pharmacokinetic Modelling of Binimetinib (PF-06811462) in Participants with BRAF V600-mutant Non-Small Cell Lung Cancer in PHAROS	Treatment-Naive 59 Previously Treated 37	PHAROS (C4221008)	
PMAR-EQDD-C422a-sNDA-1316 and erratum	Exposure-Response Analysis of Safety for Encorafenib and Binimetinib in Participants with BRAF V600-mutant NSCLC in PHAROS	Treatment-Naive 59 Previously Treated 39	PHAROS (C4221008)	
PMAR-EQDD-C422a-sNDA-1489 and erratum	Exposure-Response Analysis of Efficacy for Encorafenib and Binimetinib in Participants with BRAF V600-mutant NSCLC in PHAROS	Treatment-Naive 59 Previously Treated 39	PHAROS (C4221008)	

2.3.2. Pharmacokinetics

Bioanalytical methods

Assessment of the bioanalytical methods for determination of MEK162, Encorafenib (LGX818) and NVP-LHY746-NX-2 in human plasma used in the clinical study ARRAY-818-202 (Pfizer Study C4221008).

A Phase 2, Open-Label Study of Encorafenib + Binimetinib in Patients with BRAF V600-Mutant Non-Small Cell Lung Cancer

Blood samples for plasma PK analysis of encorafenib, its metabolite (LHY746), and binimetinib were to be collected. The blood samples were collected into K_2EDTA tubes. Further processing is not described.

The samples were stored frozen at -80°C upon arrival in Middleton. The samples were stored at -25°C prior to arrival in Middleton.

The maximum of 742 days passed between sample collection and analysis of MEK162.

The maximum of 738 days passed between sample collection and analysis of LGX818 and NVP-LHY746-NX-2.

Determination of Binimetinib (MEK162) in Human Plasma

In this study, MEK162 was determined in human plasma samples according to method P1593.02 entitled "Quantitation of MEK162 and N-Desmethyl MEK162 in Human Plasma via HPLC with MS/MS Detection". The bioanalytical part of the studies is carried out at PPD, USA.

789 samples have been analysed in 15 sequences for determination of MEK162 by HPLC/MS/MS. Six sequences included diluted samples.

Calibration and quality control standards with the concentrations given below were used for method validation and sample analysis. Each batch included calibration curve standards 1.00, 2.00, 4.00, 16.0, 60.0, 250, 800, and 1000 ng/mL), quality control samples (3.00 ng/mL, 400 ng/mL, 750 ng/mL, and 40.0 ng/mL; diluted QC: QC 3 Dil 10 - 750 ng/mL and QC 4 Dil 20 – 10000 ng/mL) and subject samples.

The calibration curves were found to be linear over the concentration range of 1.0 to 1000 ng/mL. The calibration lines of chromatographic response versus concentration were determined by the weighted least square regression analysis with a weighting factor of $1/x^2$. The coefficient of determination (r^2) was consistently > 0.998.

Between run precision and accuracy of the calibration standards ranged from 2.2 % to 4.8 % and 98.6 % to 100.7 %, respectively.

Between run precision and accuracy of the quality control samples ranged from 2.9 % to 4.1 % and 100.5 % to 102.2 %, respectively.

Between run precision and accuracy of the diluted quality control samples were 4.0 % to 7.5 % and 102.6 % to 98.1 %, respectively.

33 plasma samples were re-assayed for MEK162 (two x unacceptable internal standard response, 31 x Result above upper limit of quantitation).

To demonstrate reproducible quantitation of incurred samples in PHAROS Study, appr. 10 % of the study samples were re-assayed. 100 % of re-analysed samples had a relative percent difference between original and reassay values of less or to ± 20 %.

Chromatograms of at least 5% of all subjects analysed, the associated calibration standards, including blank standard, zero standard and QC samples as well as the calibration curves have been presented. (No chromatograms from this study were individually integrated.)

The potential for carryover from a sample containing a high concentration of analyte to the following sample in an injection sequence was monitored by injecting duplicate extracted matrix blanks immediately after the ULOQ calibration standards in each run. There were no contributions from

chromatographic peaks, at the expected retention time of the analyte in the blank samples, greater than 20% of the mean analyte response for the LLOQ calibration standards in any runs.

Each analytical run contains the following components: calibration standards, quality controls, blanks, and study samples.

Method Description P1593.02

MEK162 were determined by gradient RP-C18-HPLC/MS-MS (ESI+) using as Internal Standard (ISTD) MEK162-d_4 after SPE. The retention times and MRM transition used for the MEK162 and its ISTD are listed in Table 4.

Table 4: Transition of the MRMTransition of the MRM

Analyte	Retention time	Precursor ion [m/z]	product ion [m/z]
MEK162	~ 1.0 min	441.1	285.0
MEK162-d_4	~ 1.0 min	447.1	285.1

The suppliers for the standards are Pfizer/Array.

The calculation was carried out Standard/ISTD peak areas normalized to its ISTD peak areas curve using linear regression (weight =$1/c^2$).

Validation Results AKCN2-P1593

The method used were sufficient validated regarding sensitivity, selectivity (including haemolysis and lipemia samples), linearity in a range of 1 ng/mL to 1000 ng/mL, precision, and accuracy, batch size evaluation, recovery, matrix effect, Re-injection reproducibility, stability, carry-over, and stability. Long-term stability of analyte in human plasma [985 days at -25°C and -80°C]. The stability of both analytes in whole blood at RT is 45 min. Concomitant medications interference testing has been performed. Long-term matrix stability in human plasma containing dipotassium EDTA at -80 °C was also proven for 837 days in the presence of LGX818 and NVP-LHY746-NX-2. At -25 °C, long-term matrix stability in human plasma containing dipotassium EDTA was proven for 985 days without concomitant medications and for 371 days in the presence of LGX818 and NVP-LHY746-NX-2.

The results for Binimetinib are listed in Table 5. The results for the metabolite N-desmethyl MEK162 are not listed, as this analyte was not determined in the Pharos study.

Table 5: Validation results for Binimetinib

Parameter	**Results**
Calibration concentrations (Units)	1.00, 2.00, 4.00, 16.0, 60.0, 250.00, 800, 1000 ng/mL
Lower limit of quantification (Units)	1 ng/mL
QC concentrations (Units)	1.00, 3.00, 400 and 750 ng/mL
Between-run accuracy	Between -4.65 and 4.05 %
Between-run precision	Between 1.95 and 3.65 %
Within-run accuracy	1 ng/mL: between 1.14 and 2.51 % 3 ng/mL: between 0.883 and 8.13 % 400 ng/mL: between -5.12 and -1.77 % 750 ng/mL: between -6.42 and -2.94 %
Within-run precision	1 ng/mL: between 3.43 and 4.06 % 3 ng/mL: between 1.84 and 2.51 % 400 ng/mL: between 0.635 and 1.54 %

Parameter	Results	
	750 ng/mL: between 1.06 and 1.87 %	
	3 ng/mL	750 ng/mL
Matrix Factor (MF)	0.9998	0.9990
IS normalized MF	1.0015	1.0123
C.V.% of IS normalized MF	1.03 %	0.581%
% of QCs with >85% and <115%	100%	100%
% matrix lots with mean <80% or>120%	0%	0%
Long-term stability of the stock solution and working solutions (Maximum observed change %)	Stock solution (500 µg/mL): Confirmed up to 421 days at -25°C (5.71 %) and 25.9h at room temperature (3.30%) Working solutions (20 µg/mL): Confirmed up to 14 days at -20°C (0.937 %) and 25.9h at room temperature (0.932%)	
Short-term stability in whole blood at room temperature or at sample processing temperature. (Maximum observed change %)	Confirmed up to 45 min in ice bath -11 % and -4.76 % at 3 and 750 ng/mL, respectively	
Long-term stability in plasma (Observed change %)	Confirmed up to 985 days at -25°C and -80°C 3 ng/mL: 4.20% and 8.69 % 750 ng/mL: -9.57% and -0.84 %	
Autosampler storage stability (Observed change %)	Refer to Post-preparative stability*	
Post-preparative stability (Observed change %)	Confirmed up to 103.27 h at 2 to 8°C 3 ng/mL: 2.21 % and 750 ng/mL: -6.30 %	
Freeze and thaw stability (Observed change %)	-20 °C and -70°C, 5 cycles, 3 ng/mL: 1.14 % and 1.24 % 750 ng/mL: -5.28 % and -4.68 %	
Dilution integrity	Concentration diluted 4-fold and 25-fold Accuracy: -5.33 % and -4.80 % Precision 1.19 % and 0.531 %	

Determination of Encorafenib (LGX818) and NVP-LHY746-NX-2 in plasma in Human Plasma

In this study, LGX818 and NVP-LHY746-NX-2 was determined in human plasma samples by LC-MS/MS method. The bioanalytical part of the studies is carried out at PPD, USA.

The first date of analysis to last date of analysis was 16 April 2020 to 05 October 2022, including re-assays and ISR analysis.

789 samples have been analysed in 17 sequences for determination of LGX818 and NVP-LHY746-NX-2 by HPLC/MS/MS.

Calibration and quality control standards with the concentrations given below were used for method validation and sample analysis. Each batch included calibration curve standards for LGX818: 1.00, 2.50, 15.0, 30.0, 150, 450, 4000, and 5000 ng/mL, and for NVP-LHY746-NX-2: 2.00, 5.00, 30.0, 60.0, 300, 900, 8000, and 10000 ng/mL) quality control samples (for LGX818 1.00, 3.00, 45.0, 400, 2000, and 3750 ng/mL and for NVP-LHY746-NX-2 2.00, 5.00, 30.0, 60.0, 300, 900, 8000, and 10000 ng/mL) and subject samples. As diluted QCs were used QC 6 Dil 10: 10,000 ng LGX818/mL and 20,000 ng NVP-LHY746-NX-2/mL).

To demonstrate reproducible quantitation of incurred samples from PHAROS study, 10.5% of the study samples were re-assayed. 95.1 % of re-analysed samples had a relative percent difference between original and re-assay values, of less or equal to ± 20%. (ISR result for RLTY 105 with a relative percent difference of -76.7% for LGX818 has been observed.)

Chromatograms of at least 5% of all subjects analysed, the associated calibration standards, including blank standard, zero standard and QC samples as well as the calibration curves have been presented. (No chromatograms from this study were individually integrated.)

The results hereafter presented exclude statistical outliers.

The calibration curves LGX818 were found to be linear over the concentration range of 1.0 to 5000 ng/mL. The calibration lines of chromatographic response versus concentration were determined by the weighted least square regression analysis with a weighting factor of $1/x^2$. The coefficient of determination (r^2) was consistently > 0.997.

The calibration curves for NVP-LHY746-NX-2 were found to be linear over the concentration range of 2.00 to 10,000 ng/mL. The calibration lines of chromatographic response versus concentration were determined by the weighted least square regression analysis with a weighting factor of $1/x^2$. The coefficient of determination (r^2) was consistently > 0.997.

Between run precision and accuracy of the calibration standards for LGX818 ranged from 3.4 % to 7.8 and 99.4 % to 100.4 %, respectively.

Between run precision and accuracy of the calibration standards for NVP-LHY746-NX-2 ranged from 3.4 % to 6.0 % and 97.8 % to 101.4 %, respectively.

Between run precision and accuracy of the quality control samples for LGX818 ranged from 3.8 % to 9.1 and 98.8 % to 102.4 %, respectively.

Between run precision and accuracy of the diluted quality control samples for LGX818 (QC 6 Dil 10 = 10,000 ng/mL) for LGX818 is 6.8 % and 96.8 %, respectively.

Between run precision and accuracy of the quality control samples for NVP-LHY746-NX-2 ranged from 4.3% to 13.4% and 98.9% to 102.1% respectively.

Between run precision and accuracy of the diluted quality control samples (QC 6 Dil 10 = 20,000 ng/mL) for NVP-LHY746-NX-2 is 7.8 % and 97.9 %, respectively.

181 plasma samples were re-assayed for LGX818 (101 Result above ULoQ, 8 results due to possible carry-over result may affected, 2 x Result above upper limit of quantitation, however sample analysed in error and no reassay needed, and 3 x Excluded from calculations due to no internal standard peak detected.). From the reassayed samples, 19 plasma samples were re-assayed again (16 Result above ULoQ, 1 reassay value does not confirm original value; no reportable result, 1 result due to possible carry-over result may affected, and 1 Excluded from calculations due to no internal standard peak detected.).

8 plasma samples were re-assayed for NVP-LHY746-NX-2 (3 x due to unacceptable internal standard response, 1 x Confirmatory reanalysis performed in conjunction with investigation., 3 x no internal standard peak detected, and 1 result due to possible carry-over result may affected).

The potential for carryover from a sample containing a high concentration of analyte to the following sample in an injection sequence was monitored by injecting duplicate extracted matrix blanks immediately after the ULOQ calibration standards in each run. There were contributions from chromatographic peaks, at the expected retention time of the analyte in the blank samples, greater than 20% of the mean analyte response for the LLOQ calibration standards in the runs. All study samples

measuring above the lower limit of quantitation with a carryover contribution potential > 5% are flagged for re-assay.

Method Description P1733.00

LGX818 and NVP-LHY746-NX-2 were determined by gradient RP-C8-HPLC/MS-MS (ESI+) using as Internal Standard (ISTD) [^{13}C,$^{2}H_3$]-LGX818 and D_7-NVP-LHY746-NX-2 after Protein Precipitation Extraction in 96-well plate. The retention times and MRM transition used for LGX818 and NVP-LHY746-NX-2 and its corresponding ISTD are listed in Table 6.

Table 6: Transition of the MRM

Analyte	Retention time	Precursor ion [m/z]	product ion [m/z]
Encorafenib LGX818	~ 2.3	540.2	359.2
[^{13}C,$^{2}H_3$]-LGX818	~ 2.3	544.2	359.2
NVP-LHY746-NX-2	~ 2.1	425.1	310.1
D_7-NVP-LHY746-NX-2	~ 2.1	432.1	317.1

The suppliers for the standards are Array.

The calculation was carried out Standard/ISTD peak areas normalized to its ISTD peak areas curve using linear regression (weight =1/c^2).

Validation Results ALEY2-P1733

The methods used were sufficient validated for both analytes regarding sensitivity, selectivity (including haemolysis and lipemia samples), linearity in a range of 1 ng/mL to 1000 ng/mL, precision, and accuracy, batch size evaluation, recovery, matrix effect, Re-injection reproducibility, carry-over, and stock solution stability, post-preparation stability and freeze/thaw stability in whole blood. The validation results are presented in Table 7 and Table 8.

Long-term matrix stability in human plasma containing dipotassium EDTA at -80 °C was also proven for 838 days in the presence of MEK162 and n-desmethyl MEK162. At -25 °C, long-term matrix stability in human plasma containing dipotassium EDTA was proven for 415 days without concomitant medications and for 381 days in the presence of MEK162 and N-desmethyl MEK162.

Table 7: Validation results for encorafenib

Parameter	Results
Calibration concentrations (Units)	1.00-2.50-15.0-30.0-150-450-4000-5000 (ng/mL)
Lower limit of quantification (Units)	1 ng/mL
QC concentrations (Units)	1.00-3.00-45.0-400-2000-3750 (ng/mL)
Between-run accuracy	Between -6.74 and -3.70 %
Between-run precision	Between 1.69 and 7.47 %
Within-run accuracy	1 ng/mL: between -10.2 and 1.75 % 3 ng/mL: between -11.9 and -3.33 %

Parameter	Results
	45 ng/mL: between -4.74 and -2.96 % 400 ng/mL: between -4.83 and -2.71 % 2000 ng/mL: between -7.71 and -3.41 % 350 ng/mL: between -6.98 and -3.94 %
Within-run precision	1 ng/mL: between 2.99 and 8.16 % 3 ng/mL: between 1.43 and 3.98 % 45 ng/mL: between 0.812 and 2.16 % 400 ng/mL: between 1.23 and 1.85 % 2000 ng/mL: between 1.57 and 2.79 % 350 ng/mL: between 1.77 and 2.62 %
Matrix Factor (MF) IS normalized MF C.V.% of IS normalized MF % of QCs with >85% and <115% % matrix lots with mean <80% or>120%	Low QC (3 ng/mL) 0.9257 0.9676 2.72 % 100% 0%
	High QC (3750 ng/mL) 0.9516 1.0133 0.841% 100% 0%
Long term stability of the stock solution and working solutions (Maximum observed change %),	Stock solution (1 mg/mL): Confirmed up to 174 days at -25°C: 0.367 % Working solution (100 µg/mL): Confirmed up to 32 days at -25°C: 0.621 %
Short term stability in whole blood at room temperature or at sample processing temperature. (Maximum observed change %)	Confirmed up to 2 h at room temperature or at 2-8°C (ice bath): -3.78 % (3 ng/mL) and 3.63 % (3750 ng/mL)
Long term stability in plasma (Observed change %)	Confirmed up to at least 415 days at -25°C and -80°C 3 ng/mL: 1.08% and 1.98 % 3750 ng/mL: 3.77% and 4.32 % In presence of binimetinib and its N-desmethyl metabolite

Parameter	Results
	Confirmed up to at least 381 days at -25°C and -80°C 3 ng/mL: -9.31 % and 1.79 % 3750 ng/mL: 2.75% and -0.426%
Autosampler storage stability (Observed change %)	Refer to post-preparative stability*
Post-preparative stability (Observed change %)	Confirmed up to 98.88 h at 2 to 8°C 3 ng/mL: -0.714% and 3750 ng/mL: -3.85 %
Freeze and thaw stability (Observed change %)	-25 °C and -80°C, 5 cycles, 3 ng/mL: -6.70 % and -7.51 % 3750 ng/mL: -6.18 % and -8.83 %
Dilution integrity	Concentration diluted 2-fold and 20-fold Accuracy: -5.38 % and 0.0678 % Precision 1.74 and 0.549 %

* In addition, a reinjection reproducibility test was performed. The reinjected run met the acceptance criteria of the original run.

Table 8: Validation results for LHY746

Parameter	Results	
Calibration concentrations (Units)	2.00-5.00-30.0-60.0-300-900-8000-10000 (ng/mL)	
Lower limit of quantification (Units)	2 ng/mL	
QC concentrations (Units)	2.00-6.00-90.0-800-4000-7500 (ng/mL)	
Between-run accuracy	Between -7.12 and -3.52 %	
Between-run precision	Between 1.76 and 5.85 %	
Within-run accuracy	2 ng/mL: between -7.82 and 1.69 % 6 ng/mL: between -11.7 and -0.317 % 90 ng/mL: between -5.19 and -4.26 % 800 ng/mL: between -5.66 and -4.17 % 4000 ng/mL: between -8.57 and -5.45 % 7500 ng/mL: between -7.83 and -4.81 %	
Within-run precision	2 ng/mL: between 1.28 and 6.21 % 6 ng/mL: between 1.31 and 6.01 % 90 ng/mL: between 0.849 and 3.63 % 800 ng/mL: between 1.49 and 2.23 % 4000 ng/mL: between 1.14 and 3.19 % 7500 ng/mL: between 1.98 and 2.69 %	
	Low QC (6 ng/mL)	High QC (7500 ng/mL)
Matrix Factor (MF)	0.9501	0.9266
IS normalized MF	0.9962	1.0046

Parameter	Results	
C.V.% of IS normalized MF	1.41%	0.505%
% of QCs with >85% and <115%	100%	100%
% matrix lots with mean <80% or>120%	0%	0%
Long term stability of the stock solution and working solutions (Maximum observed change %),	Stock solution (1 mg/mL): Confirmed up to 174 days at -25°C: (0.927 %) Working solution (200 µg/mL): Confirmed up to 32 days at -20°C: (1.56 %)	
Short-term stability in whole blood at room temperature or at sample processing temperature. (Maximum observed change %)	Confirmed up to 2 h at room temperature or at 2-8°C (ice bath): 6 ng/mL: 3.83 % 7500 ng/mL: 2.11%	
Long term stability in biological matrix (Observed change %)	Confirmed up to at least 415 days at -25°C and -80°C 6 ng/mL: 1.21 % and 0.88 % 7500 ng/mL: -1.09% and -0.11 % In presence of binimetinib and its N-desmethyl metabolite Confirmed up to at least 381 days at -25°C and -80°C 6 ng/mL: -5.84 % and 2.09 % 7500 ng/mL: 2.69% and -1.28%	
Autosampler storage stability (Observed change %)	Refer to post-preparative stability*	
Post-preparative stability (Observed change %)	Confirmed up to 98.88 h at 2 to 8°C 6 ng/mL: 0.770% and 7500 ng/mL: -4.30 %	
Freeze and thaw stability (Observed change %)	-25 °C and -80°C, 5 cycles, 6 ng/mL: -8.32 % and -8.39 % 7500 ng/mL: -7.35 % and -10.0 %	
Dilution integrity	Concentration diluted 2-fold and 20-fold Accuracy: -7.45 % and -1.56 % Precision: 2.01 and 0.576 %	

* In addition, a reinjection reproducibility test was performed. The reinjected run met the acceptance criteria of the original run.

Pharmacokinetics in the target population

Only the new PK data from study C4221008 (PHAROS) relevant to this extension of indication for patients with advanced NSCLC are presented.

PK was investigated after single and multiple doses in the PHAROS study. Blood samples for plasma PK analysis of encorafenib, its metabolite (LHY746), and binimetinib were collected 0.5, 1.5, 3, and 6 hours post-dose on C1D1 (Cycle 1 Day 1) and C1D15 and predose on C1D15 and C2D1 (For participants enrolled under CSP Versions 0 to 3). For participants enrolled under CSP Version 4 or later, only sparse blood samples were collected pre-dose (within 30 minutes) on Day 1 of Cycles 1-6.

A total of 97 out of 98 participants in the Safety Set were included in the PK Analysis Set, among which 79 participants had serial PK sampling. Summaries of selected PK parameters from the full sampling group for encorafenib, LHY746 and binimetinib, separated for line of therapy, are presented in the following.

In patients with NSCLC, observed **encorafenib** parameters calculated by non-compartmental approach (NCA) were grossly comparable with PK parameters observed in patients with melanoma at the same doses (Figure 3 and Table 9). Encorafenib median Tmax on C1D1 was 1.5 h in treatment-naïve patients and 2.87 h in previously treated patients, and 1.5 hours in both groups on C1D15. The geometric LS mean encorafenib accumulation ratios were 0.500 and 0.393, respectively. The reduced systemic exposures of encorafenib on C1D15 compared to those on C1D1 are attributed to the auto-induction of CYP3A4.

Figure 3: Encorafenib: Comparison of PK Parameters at steady state (geometric mean and range, log-y-scale for Ctrough) observed in ARRAY-818-202 Study (NSCLC), ARRAY-818-103 and CMEK162X2110 (melanoma and other solid tumours), CMEK162B2301 and CLGX818X2109 (melanoma)

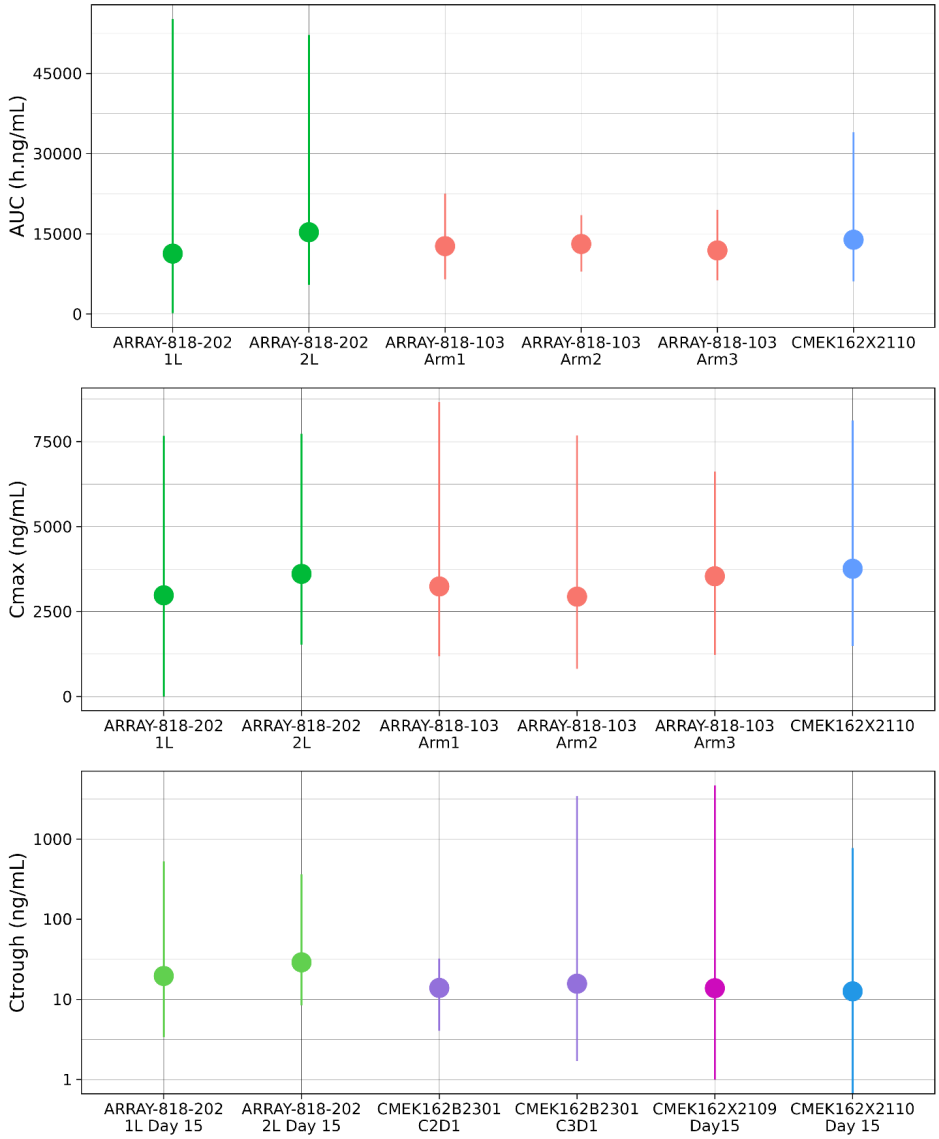


Table 9: Encorafenib: Descriptive Statistics of AUC, Cmax and Ctrough Observed on Day 1 and Day 15 (Steady State) in Patients with BRAF V600-mutant NSCLC (ARRAY-818-202/C4221008) and in Patients with BRAF V600-mutant melanoma

Study	Tumour	AUC (h.ng/mL)		Cmax (ng/mL)		Ctrough (ng/mL)	
		Day 1	Day 15	Day 1	Day 15	Day 1	Day 15
ARRAY-818-202/ C4221008 Treatment Naive	NSCLC	AUC0-6 21200 (47.1) (N=48) [3600, 52900]	AUC0-6 8000 (119) (N=39) [44.2, 25700] AUCtau 11300 (96.8) (N=38) [163, 55200]	6350 (49.3) (N=50) [1020, 16900]	2980 (149) (N=39) [7.33, 7670]	NA	19.6 (110) (N=38) [3.39, 526]
ARRAY-818-202/ C4221008 Previously Treated		AUC0-6 22400 (46.9) (N=22) [5730, 43100]	AUC0-6 10500 (65.8) (N=11) [4310, 24700] AUCtau 15300 (81.9) (N=11) [5480, 52200]	5960 (57.7) (N=23) [1470, 12100]	3610 (56.3) (N=11) [1530, 7730]	NA	29 (142) (N=11) [8.42, 365]
CMEK162 X2110	Melanoma and Solid Tumours	32200 (53.7) (N=13) [16900, 67200]	13900 (58.9) (N=11) [6140, 34000]	7040 (41.7) (N=13) [4670, 14900]	3760 (62.6) (N=11) [1490, 8120]	NA	13.9 (82.2) (N=11) [4.07, 32.3]
ARRAY-818-103 Arm 1	Melanoma and Solid Tumours	24500 (36.7) (N=20) [10100, 50600]	12700 (37.6) (N=20) [6520, 22500]	6150 (41.9) (N=20) [3490, 16500]	3240 (55.7) (N=20) [1190, 8660]	NA	ND
ARRAY-818-103 Arm 2		AUClast 25900 (61.7) (N=10) [8260, 56700]	AUClast 13100 (28.6) (N=10) [7940, 18500]	6060 (77.7) (N=10) [1500, 16100]	2940 (72.2) (N=10) [817, 7680]	NA	ND
ARRAY-818-103 Arm 3		NA	AUClast 11900 (35.8) (N=11) [6300, 19500]	NA	3540 (55.6) (N=11) [1230, 6620]	NA	ND
CMEK162 B2301	Melanoma	ND	ND	ND	ND	C2D1 (N=119) 15.7 (240) [1.70, 3430] C3D1 (N=98) 13.8 (227) [1.00, 4670]	
CMEK162 X2109	Melanoma	ND	ND	ND	ND	12.6 (102.9) (N=117) [0, 772]	

In Study ARRAY-818-103, AUC=AUClast, in Study CMEK162X2110: AUC=AUCtau. Descriptive statistics as Geometric mean (geometric CV%) and [range] (N= number of participants with non-missing values); NA: not applicable; ND: not determined.

In patients with NSCLC, observed **LHY746** metabolite non-compartmental PK parameters were similar with PK parameters observed in patients with melanoma at the same doses (Table 10and Table 11).

LHY746 median Tmax on C1D1 was ~5.7 h; and 3.0 hours on C1D15, both in treatment-naïve and in previously treated patients.

Table 10: Summary of plasma LHY746 PK parameters by visit and line of therapy (PK analysis set)

	Treatment Naïve				Previously Treated				Total			
Parameter (units)	**n**	**C1D1 (N=50)**	**n**	**C1D15 (N=39)**	**N**	**C1D1 (N=23)**	**n**	**C1D15 (N=11)**	**n**	**C1D1 (N=73)**	**n**	**C1D15 (N=50)**
AUC_{0-6} (ng•hr/mL)	48	3180 (66.1)	39	10600 (77.8)	22	3200 (69.1)	11	11800 (52.5)	70	3190 (66.4)	50	10800 (72.1)
AUC_{tau} (ng•hr/mL)	NA	NA	38	30200 (77.2)	NA	NA	11	34300 (56.8)	NA	NA	49	31000 (72.4)
C_{max} (ng/mL)	50	794 (58.9)	39	2320 (82.3)	23	781 (63.7)	11	2500 (56.0)	73	790 (59.9)	50	2350 (76.2)
C_{trough} (ng/mL)	NA	NA	38	516 (89.4)	NA	NA	11	607 (88.8)	NA	NA	49	536 (88.5)

Table 11: Descriptive Statistics of LHY746/encorafenib ratios and LHY746 Accumulation Ratios Observed on Day 15 (steady-state) in Patients with BRAF V600-mutant NSCLC (ARRAY-818-202/C4221008) and in Patients with BRAF V600-mutant Melanoma

Study	Tumour	MR AUC[1]	MR Cmax	Rac Cmax	Rac AUC[1]
ARRAY-818-202/C4221008 Treatment Naive	NSCLC	1.68 (67.2) (N=39) [0.652, 11.1]	0.987 (67.2) (N=39) [0.377, 11.3]	2.93 (2.41, 3.57) (N=39)	3.32 (2.70,4.08) (N=39)
ARRAY-818-202/C4221008 Previously Treated		1.42 (52.5) (N=11) [0.673, 3.21]	0.878 (34.8) (N=11) [0.522, 1.48]	3.40 (2.51, 4.62) (N=11)	3.75 (2.61, 5.39) (N=11)
ARRAY-818-103 Arm 1 Day 15	Melanoma and Solid Tumours	3.40 (55.9) (N=20) [1.38, 7.40]	0.978 (49.9) (N=20) [0.335, 1.92]	2.64 (60.4) (N=20) [0.697, 10]	6.62 (66.3) (N=20) [2.36, 29.1]
ARRAY-818-103 Arm 2		3.19 (44.0) (N=10) [1.41, 5.54]	1.01 (30.2) (N=10) [0.609, 1.62]	2.46 (59.7) (N=10) [0.733, 5.39]	6.57 (63.8) (N=10) [2.29, 16.2]
ARRAY-818-103 Arm 3		4.62 (43.3) (N=11) [2.20, 7.83]	1.13 (77.6) (N=11) [0.422, 4.80]	ND	ND

Source:
[1]AUC = AUC0-6 for ARRAY-818-202 and AUClast for ARRAY-818-103.
Descriptive statistics correspond to geometric mean (geometric CV) (N=number of participants with non-missing values) and [range] except for Rac in ARRAY-818-202: ratio of geometric mean (90% confidence interval); ND: not determined

Observed **binimetinib** parameters in patients with NSCLC calculated by non-compartmental approach were similar to PK parameters observed in patients with BRAF-mutant metastatic melanoma at the same doses (Figure 4 and Table 12). The geometric LS mean binimetinib accumulation ratios were 0.859 and 0.850, respectively, consistent with the relatively short half-life of binimetinib. Binimetinib median Tmax on C1D1 and on C1D15 was ~1.5 h, both in treatment-naïve and in previously treated patients.

Figure 4: Binimetinib: Comparison of PK Parameters at steady state (geometric mean and range) observed in Studies ARRAY-818-202 (NSCLC), ARRAY-818-103 and CMEK162X2110 (melanoma and solid tumours), CMEK162B2301 and CLGX818X2109 (melanoma)

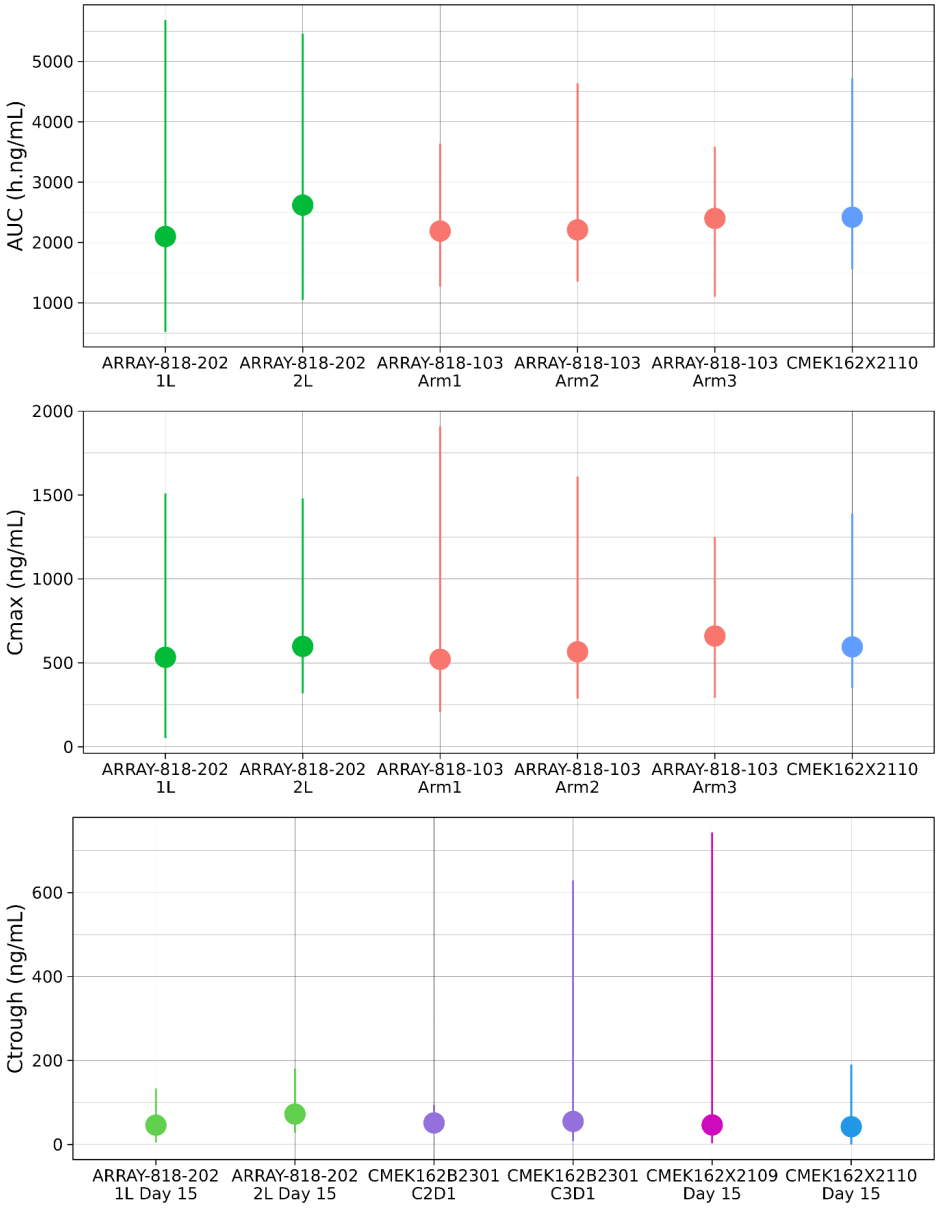


Table 12: Binimetinib: Descriptive Statistics of AUC, Cmax and Ctrough Observed on Day 15 (Steady State) in Patients with BRAF V600-mutant NSCLC (ARRAY-818-202/C4221008) and in Patients with BRAF V600-mutant Melanoma

Study	Tumour	AUC (h.ng/mL)		Cmax (ng/mL)		Ctrough (ng/mL)	
		Day 1	Day 15	Day 1	Day 15	Day 1	Day 15
ARRAY-818-202/ C4221008 Treatment Naive	NSCLC	AUC0-6 1920 (58.2) (N=50) [470, 7290]	AUC0-6 1600 (48.4) (N=41) [272, 4330] AUCtau 2100 (44.5) (N=40) [520, 5690]	636 (64.9) (N=52) [137, 2480]	533 (63.3) (N=41) [51.3, 1510]		46.0 (68.7) (N=40) [5.08, 133]
ARRAY-818-202/ C4221008 Previously Treated		AUC0-6 2030 (60.1) (N=22) [697, 4000]	AUC0-6 1920 (51.1) (N=11) [820, 3450] AUCtau 2620 (54.9) (N=11) [1050, 5460]	642 (73.8) (N=23) [169, 1720]	598 (54.4) (N=11) [319, 1480]		72.5 (62.8) (N=11) [28.1, 181]
CMEK162 X2110	Melanoma and Solid Tumours	2390 (48.2) (N=11) [1510, 5890]	2420 (33.9) (N=11) [1560, 4720]	735 (45.4) (N=13) [410, 1820]	595 (39.0) (N=11) [349, 1390]		51.4 (41.6) (N=11) [27.6, 94.8]
ARRAY-818-103 Arm 1	Melanoma and Solid Tumours	2290 (43.3) (N=20) [1200, 7120]	2190 (33.8) (N=20) [1270, 3640]	661 (55.1) (N=20) [301, 2180]	521 (59.9) (N=20) [206, 1910]	ND	
ARRAY-818-103 Arm 2		2040 (81.0) (N=10) [381, 5180]	2210 (40.7) (N=10) [1350, 4640]	549 (89.5) (N=10) [91.8, 1420]	566 (63.1) (N=10) [287, 1610]	ND	
ARRAY-818-103 Arm 3		NA	2400 (38.6) (N=11) [1100, 3590]	NA	660 (39.7) (N=11) [291, 1250]	ND	
CMEK162 B2301	Melanoma	ND		ND		C2D1 (N=77) 55.0 (91.9) [8.16, 629] C3D1 (N=66) 46.5 (92.0) [2.57, 743]	
CMEK162 X2109	Melanoma	ND		ND		42.4 (62.2) (N=111) [0, 191]	

In Study ARRAY-818-103, AUC=AUClast, in Study CMEK162X2110: AUC=AUCtau. Descriptive statistics as Geometric mean (geometric CV%) and [range] (N= number of participants with non-missing values); NA: not applicable; ND: not determined.

Special populations

Pharmacokinetics in sub-populations were evaluated through **population PK analysis** performed on data from PHAROS (Reports PMAR-EQDD-C422a-sNDA-1467 encorafenib and PMAR-EQDD-C422a-sNDA-1468 binimetinib with Erratum reports).

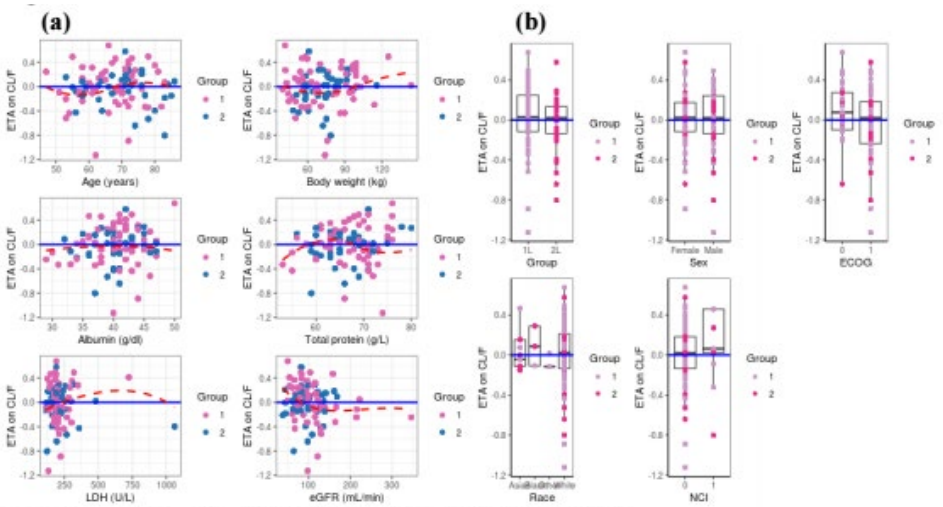
Encorafenib

Table 13: Final model parameters estimates

Parameter	Estimate	RSE (%)	Shrinkage (%)	95% CI
$\theta_{\text{Duration-z (h)}}$	1.683	6.726	-	(1.461 ; 1.905)
$\theta_{\text{CL/F Day 1}}(L/h)$	12.978	6.795	-	(11.250 ; 14.707)
$\theta_{\text{V2/F}}(L)$	33.492	13.726	-	(24.482 ; 42.503)
$\theta_{\text{Q/F}}(L/h)$	2.331	36.748	-	(0.652 ; 4.010)
$\theta_{\text{V3/F}}(L)$	56.096	46.605	-	(4.855 ; 107.336)
$\theta_{\text{Fraction-z}}$	0.656	3.068	-	(0.617 ; 0.696)
$\theta_{\text{Prop error}}$	0.596	3.807	-	(0.552 ; 0.641)
$\theta_{\text{Add error}}$	13.050	27.461	-	(6.026 ; 20.073)
$\theta_{\text{CL/F ss}}(L/h)$	40.222	6.765	-	(34.889 ; 45.556)
$\theta_{\text{Lag time (h)}}$	0.452	4.419	-	(0.413 ; 0.491)
$\theta_{\text{Age on CL/F}}$	-1.419	24.613	-	(-2.103 ; -0.734)
IIV	**CV (%)**	**RSE (%)**	**Shrinkage (%)**	**95% CI**
IIV on $\theta_{\text{CL/F}}(\%)$	36.74	22.873	15.881	(27.39 ; 44.27)
IIV on $\theta_{\text{V2/F}}(\%)$	68.04	23.982	17.459	(49.5 ; 82.52)
OFV	9654.862	-	-	-

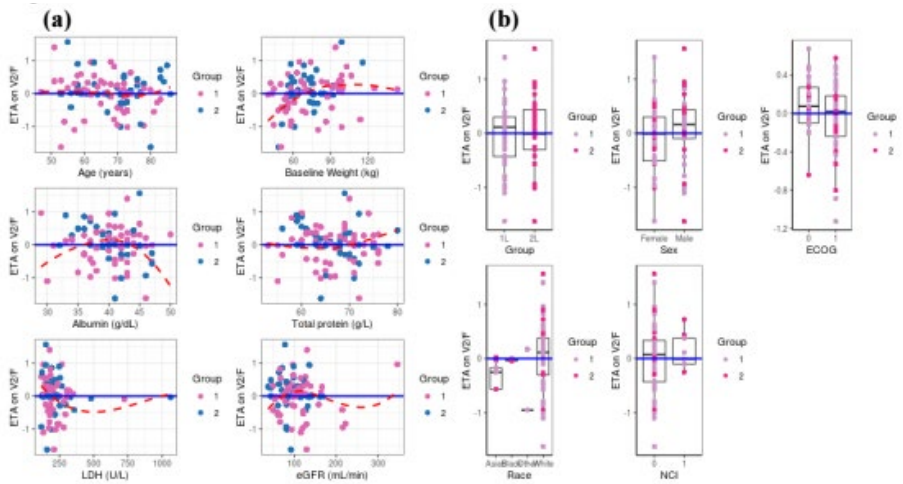
Repository artifact ID FI-36794550. Line 1 substituted.
The 95% CIs were calculated based on standard errors from the NONMEM covariance step.
IIV on CL/F was shared for CL/F Day 1 and CL/Fss.
Table abbreviations: CI=confidence interval; CL/F Day 1=apparent initial clearance; V_2=central volume of distribution; Q/F=apparent inter-compartmental clearance; V_3=peripheral volume of distribution; Fraction-z=fraction of the dose is absorbed by zero-order kinetics during a given period of time; Duration-z=duration of zero-order absorption; CL/Fss=apparent steady-state induced clearance; CV=coefficient of variation; Prop=proportional; Add=additive; IIV=inter-individual variability; OFV=objective function value; RSE=relative standard error.

Figure 5: Final model ETAs on clearance of Encorafenib versus baseline covariates



Repository artifact ID: (a) FI-36437365 and (b) FI-36437369.

Figure 6: Final model ETAs on volume of distribution versus baseline covariates



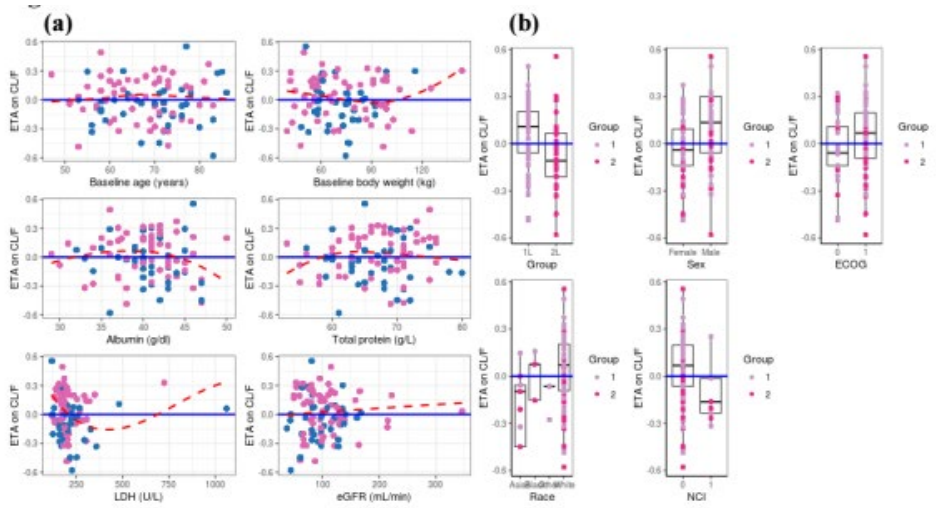
Repository artifact IDs: (a) FI-36437367 and (b) FI-36437371.

Binimetinib

Table 14: Final model parameters estimates

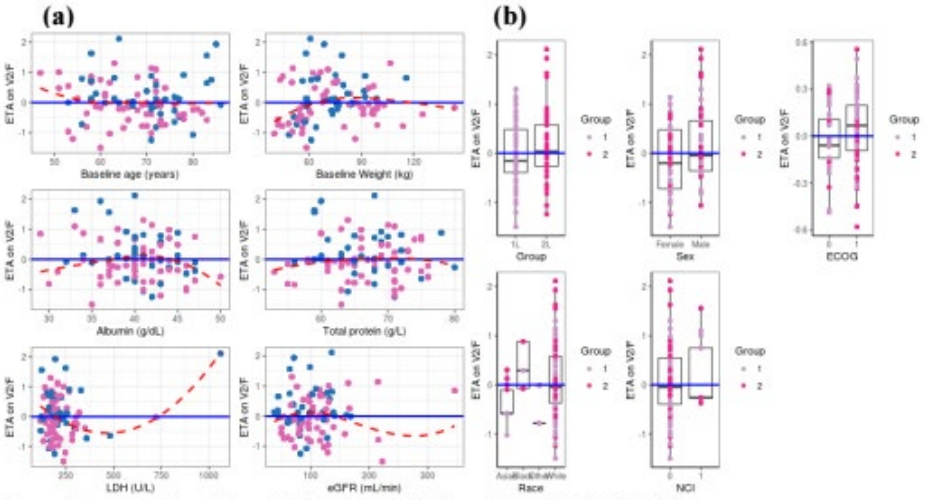
Parameter	Estimate	RSE (%)	Shrinkage (%)	95% CI
$\theta_{\text{Duration-z (h)}}$	2.087	7.189	-	(1.812 ; 2.367)
$\theta_{\text{CL/F}}(L/h)$	17.115	3.627	-	(15.904 ; 18.433)
$\theta_{\text{V2/F}}(L)$	16.459	16.790	-	(12.133 ; 21.647)
$\theta_{\text{Q/F}}(L/h)$	1.210	77.239	-	(0.169 ; 2.473)
$\theta_{\text{V3/F}}(L)$	35.958	56.464	-	(8.970 ; 86.982)
$\theta_{\text{Fraction-z}}$	0.700	3.153	-	(0.662 ; 0.733)
$\theta_{\text{Prop error}}$	0.453	4.555	-	(0.420 ; 0.489)
$\theta_{\text{Add error}}(ng/mL)$	19.298	13.995	-	(16.435 ; 23.141)
$\theta_{\text{Age on CL/F}}$	-1.120	26.039	-	(-1.653 ; -0.568)
$\theta_{\text{BWT on CL/F}}$	0.742	18.071	-	(0.490 ; 1.011)
IIV	CV (%)	RSE (%)	Shrinkage (%)	95% CI
IIV on $\theta_{\text{CL/F}}(\%)$	28.11	18.127	17.701	(23.45 ; 33.62)
IIV on $\theta_{\text{V2/F}}(\%)$	84.38	22.982	16.459	(70.07 ; 102.08)
OFV	7393.821	-	-	-

Figure 7: Final model ETAs on clearance of binimetinib versus baseline covariates



Repository artifact ID: (a) FI-36525026 and (b) FI-36525030.

Figure 8: Final model ETAs on volume of distribution versus baseline covariates



Repository artifact IDs: (a) FI-36525026 and (b) FI-36525030.

Based on the population PK analysis, age was the only covariate found to be a statistically significant predictor of encorafenib exposure. The median age was about 65 years (range 47-86). The predicted impact of age resulted in a ~ 1.6 higher and ~ 0.7 lower clearance in a 47-year-old-and 86-years-old patient than a typical patient, respectively. However, in the previous population analyses in melanoma (median 55 years and range [19.0-94.0]) and mCRC (58.0 years [19.0-89.0]), age was selected as a significant covariate on CL/F and V/F, but more limited differences were observed on PK parameters in these larger populations with a larger age range (Reports T2019-00140 and T2019-00141).

Similarly, regarding age, the predicted impact also resulted in a ~ 1.5 higher and ~ 0.7 lower clearance of binimetinib than a typical patient. The estimated covariate coefficient was -1.12 and is larger than age covariate estimates in previous population PK models equal to -0.02 and -0.183 in models with binimetinib monotherapy and in combination with encorafenib, respectively. No major effect of age on CL/F was identified in previous population PK analyses with larger datasets. A maximum difference of 11% on CL/F at 5th and 95th percentiles compared to the median was predicted. In these models, the age spread was larger than the current analysis integrating NSCLC patients: 27-79 years-old in Report CP16-001 (5th and 95th percentiles) and 19-89 years-old in Report CP17-004 (range).

Baseline eGFR (range: 38-346 mL/min/1.73m^2) was considered not a significant covariate on encorafenib and binimetinib elimination, consistent with prior data that had indicated minimal renal clearance of encorafenib and no clinically significant differences in PK of binimetinib based on mild, moderate or severe RI.

Similarly, baseline AST and baseline total bilirubin laboratory values were not significant covariates on encorafenib and binimetinib elimination, also consistent with previous data that indicated no clinically significant differences in PK of encorafenib and binimetinib for mild hepatic impairment (NCI-ODWG criteria).

In addition, none of the following intrinsic or extrinsic factors evaluated had a significant impact on encorafenib or binimetinib PK: baseline body weight, sex, total protein, albumin, LDH, ECOG Performance Status, smoking status or line of therapy (1L versus 2L).

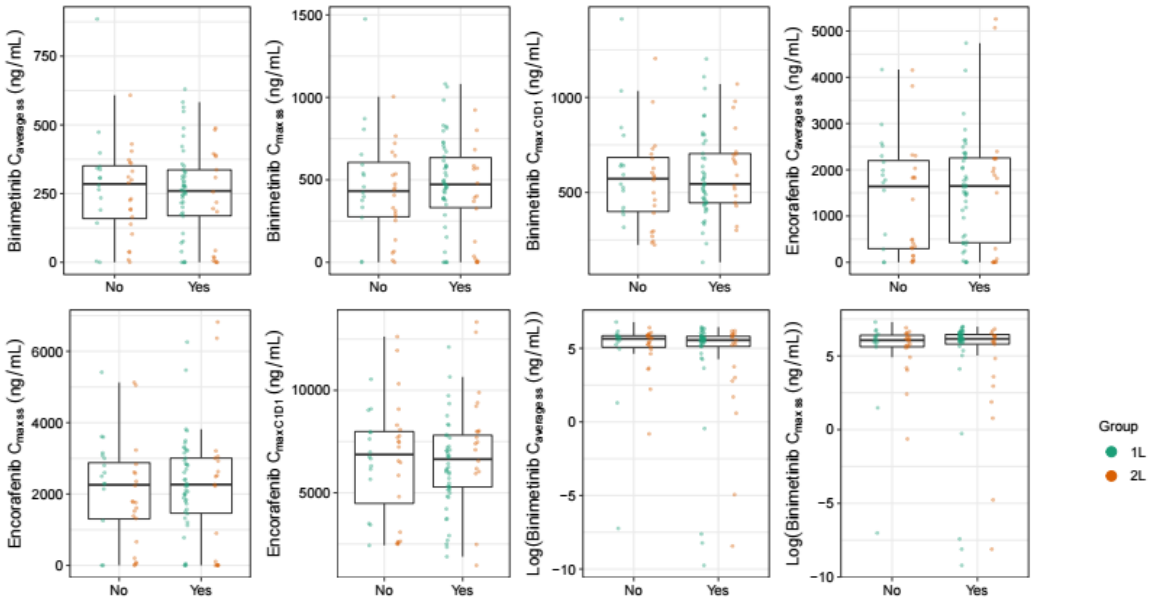
2.3.3. PK/PD modelling

No PK/PD relationship analysis for biomarkers were performed.

ERR for efficacy (Report PMAR-EQDD-C422a-sNDA-1469 with Erratum report)

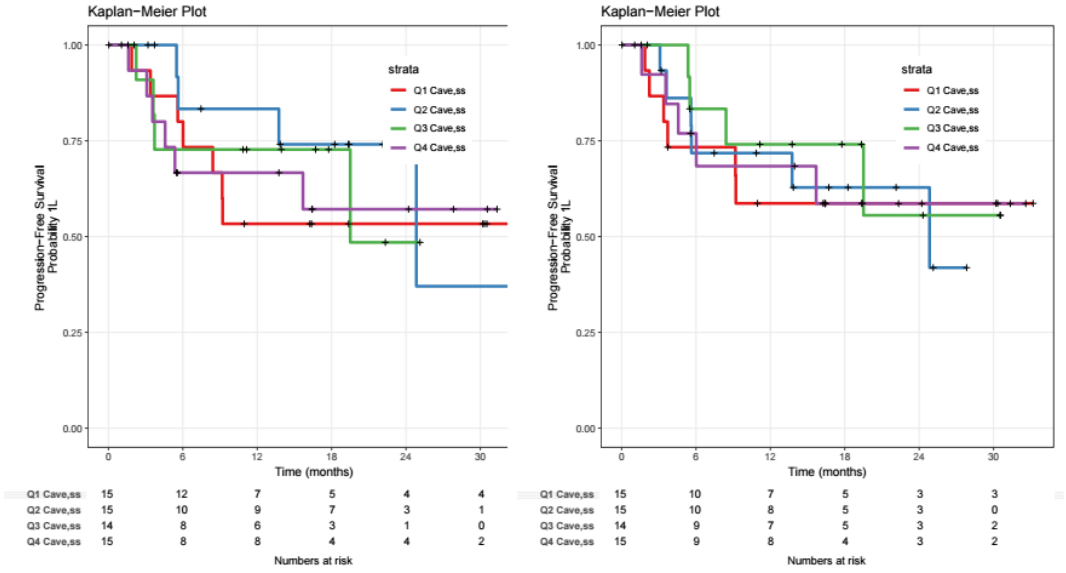
The exposure-response analysis for ORR (Figure 9 below) and PFS (Figure 10 below) for treatment-naïve/1L and previously treated/2L participants indicated no statistically significant exposure-response relationship for either drug substance.

Figure 9: Objective Response Rate by Encorafenib and Binimetinib Exposures



Source: derived from PMAR-EQDD-C422a-sNDA-1489 Figure 1

Figure 10: PFS for 1L patients in PHAROS by exposure quartile



(a) FI-36552568 **(b)** FI-36552565

Repository artifact IDs are shown in subfigure labels.

Figure Abbreviations: PFS = progression-free survival; Q1 = Cycle 1 Day 15 average concentration, first quartile; Q2 = Cycle 1 Day 15 average concentration, second quartile; Q3 = Cycle 1 Day 15 average concentration, third quartile; Q4 = Cycle 1 Day 15 average concentration, fourth quartile.

Left: encorafenib, right: binimetinib

For 2L patients, an increase in baseline haemoglobin was associated with an increased probability of experiencing a PR or better (Figure 11 below). The exposure-PFS results for 2L participants indicated that higher haemoglobin values (median 121.0 g/l; range: 59, 161 g/l) were associated with a higher probability of a longer PFS. However, when stratified by haemoglobin quartile (Figure 12 below), while there is a general consistent trend, i.e., increasing probability of PFS with increasing haemoglobin, there is a lot of overlap in the predicted PFS and, given the low number of PFS events in the 2L analysis population, results should be interpreted with caution.

Figure 11: Simulation for all covariates and Objective Response Rate PR or Better

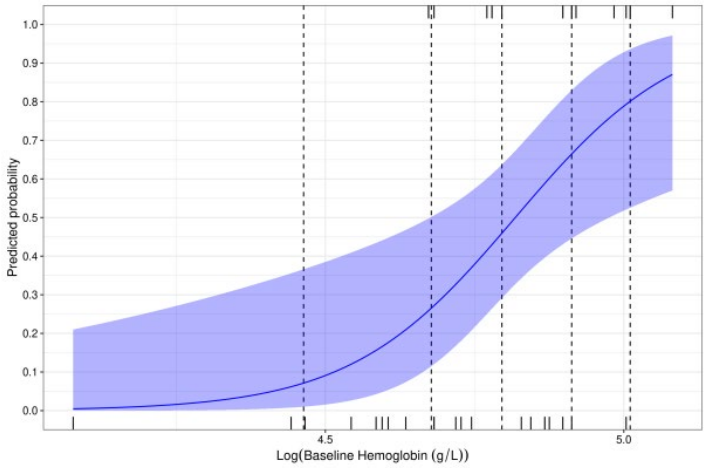
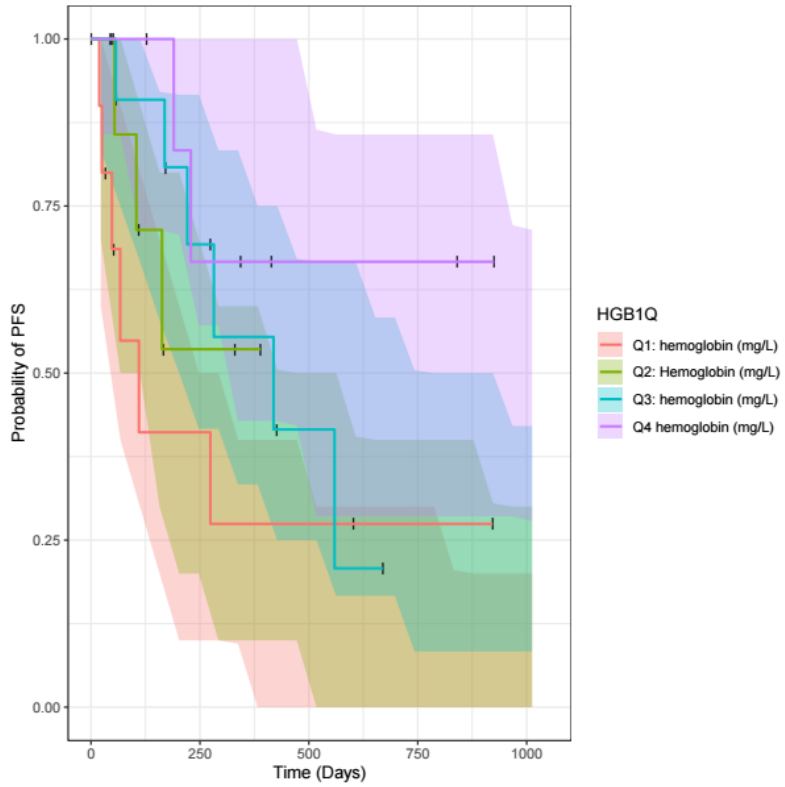


Figure 12: Base progression free survival by haemoglobin quartile in 2L participants from PHAROS



Repository artifact ID FI-36554701.

The following covariates were not identified as predictors of PFS: sex, age, baseline body weight, baseline ECOG performance status, and baseline laboratory values of albumin, AST, ALP, and LDH.

ERR for Safety (Report PMAR-EQDD-C422a-sNDA-1316 with Erratum)

There were no statistically significant E-R relationships identified between either encorafenib or binimetinib and all grades diarrhoea, fatigue, vomiting, anaemia, constipation, or dyspnoea. Nor was there a statistically significant E-R relationship identified between either encorafenib or binimetinib and all AE grades 3 or worse. There was only a statistically significant E-R relationship identified between binimetinib and nausea all grades (Odds Ratio: 11.6, corresponding to a 1-unit change in Log(Binimetinib Cmax C1D1 (ng/mL)) while all other covariates in the model are held constant).

2.3.4. Discussion on clinical pharmacology

Based on the data from the pivotal study (PHAROS), the MAH submitted a pop PK modelling of encorafenib, binimetinib and two exposure response analyses.

After introduction of amendment 4 to Pharos study protocol, PK sampling was reduced from intensive sampling to sparse (pre-dose on Day 1 of Cycles 1-6). According to the MAH, 79 of 98 patients had intensive blood sampling. The PK values provided in Table 9 and Table 12 were derived only from the full PK sampling group, which states a total of n=73 patients for encorafenib and n=75 for binimetinib.

From the tables in the popPK/ERR reports, it can be derived that overall 59 treatment naive and 39 pre-treated patients contributed PK data. This means that only 11% (7/59) of treatment-naïve patients but 41% (16/39) pre-treated patients were included after implementation of CSP amendment V4 (with

sparse PK sampling).As a consequence, a relatively low number of patients in the pre-treated subgroup had a full PK sampling and were used for the PK analyses.

For encorafenib 450 mg QD, exposure as of AUC, Cmax and Ctrough were about 20% to 50% higher in pre-treated NSCLC patients compared to treatment-naïve patients.

The highly variable Ctrough levels of 19.6 and 29.0 ng/ml (naïve and pre-treated NSCLC, resp.) on C1D15 are in a comparable range, though up to 2-fold higher than in melanoma patients. To contextualise, at C3D1 geo-mean Ctrough for 450mg had been 13.8ng/ml in study CMEK162B2301 (Columbus, melanoma) with a strong drop from the first day due to auto-induction of CYP3A4.

It is also noted that from Day 1 to Day 15 the variability CV% of the exposure parameters for encorafenib in treatment-naïve patients increased more than 2-fold, in contrast to those of the pre-treated subgroup.

For binimetinib 45 mg BID, exposure as of AUC and Cmax was also higher in pre-treated NSCLC patients. Variability was comparable between D1 and D15.

Ctrough was increased by about 60% in pre-treated patients (72.5ng/ml) vs. naïve patients (46.0ng/ml). To contextualise, as derived from data of melanoma study X2110/phase IB (Table 12) Ctrough,ss of binimetinib at C1D15 was 51.4ng/ml.

While steady-state primary PK parameters of encorafenib, LHY746 and binimetinib seem overall in the same ranges for the total NSCLC population vs the melanoma population (study X2110/phase IB) at the same doses, the variability of the PK results is much higher (2-fold); however this is probably due to the differences observed between the treatment-lines.

For encorafenib's metabolite LHY746, exposure was overall more comparable between treatment lines. However, for the metabolite the AUC accumulation ratio and the M:P ratio was only about a half of those observed in the earlier melanoma studies.

The potential reasons for the observed differences in exposures and variability between 1L and 2L treatment-lines and C1D1/D15 as well as the differences observed for the metabolite accumulation, including intrinsic and extrinsic factors were discussed. Data provided show some differences in demographics of the 1L and 2L populations: 2L patients being slightly older and with a lower body weight, which could have contributed to higher mean exposures and a higher variability of encorafenib in these patients.

Patients with mild hepatic impairment (as of NCI classification) were included and in both 1L and 2L groups, patients concomitantly took strong CYP3A4 inhibitors, factors known to increase exposure of encorafenib. However, it seems that these factors had less effect on exposure in the 1L group.

From the very limited overall number of patients, any further conclusions related to the NSCLC study population, would be arbitrary. Nevertheless, it can be emphasized that a combination of these intrinsic and extrinsic factors would probably result in particularly high exposures and higher variability and could be relevant for safety (See safety in special population).

From the additional analyses for binimetinib the observed differences between the treatment naïve and pre-treated NSCLC patients populations, and the melanoma patients are likely to be resulting from the above mentioned high variability within the dataset (also related to the limited number of patients in the pre-treated NSNCLC dataset), and some differences in the demographic characteristics, rather than a true effect from underlying disease or line of treatment.

Population PK analysis estimated only age as significant covariate on encorafenib and binimetinib exposure, however this was not considered clinically relevant and no dose adjustment for age is proposed. Further analyses of underlying baseline factors, such as weight, or renal or hepatic function

were conducted supporting the absence of confounding covariates impacting age in the population PK analyses for both encorafenib and binimetinib (data not shown).

Based on popPK, CL/F of binimetinib was lower in the 2L subgroup (as well as Asian patients and those with hepatic function NCI score 1 see Figure 7-b [CAVE: very small patient numbers]), which corresponds to the non-compartmental analysis (NCA) results of higher exposure in this patient subgroup.

Exposure-response analyses could not provide relevant information, as only one dose level for encorafenib 450 mg QD and binimetinib 45 mg BID was investigated, limiting the evaluable exposure range in general.

Therefore, no difference in ORR or PFS for treatment-naïve/1L patients between responders and non-responders could be observed.

For pre-treated/2L patients, despite the higher exposure compared to 1L, no differences in achievement of response depending on binimetinib or encorafenib exposure were observed in the ER analysis.

The ER analysis found, however, a positive correlation of haemoglobin with response and PFS in this pre-treated patient group. This finding corresponds well to the clinical efficacy information, in that the response rate was lower in CTx-pretreated patients, who commonly suffer from anaemia, compared to patients without chemotherapy. Still, this result was obviously not correlated to any drug exposure, as low haemoglobin is a known negative prognostic factor in NSCLC patients.

No ER correlation for safety was found for encorafenib. Only binimetinib showed a correlation to all-grade nausea for LogCmaxC1D1, but nausea is already a very common known adverse reaction of binimetinib treatment.

2.3.5. Conclusions on clinical pharmacology

The clinical pharmacology evaluation from the small SAT in NSCLC patients showed no clinically significantly different results compared to the previous melanoma population, at the same doses of 450 mg QD encorafenib and 45 mg BID binimetinib.

From this one investigated dose level, no clinically relevant conclusions for exposure-response on either efficacy or safety could be drawn.

The data provided can support the extension of the indication to NSCLC patients.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose-selection study was performed specifically for the development of encorafenib and binimetinib in NSCLC. The approved efficacious and safe doses and administration schedule of encorafenib 450 mg orally QD in combination with binimetinib 45 mg orally BID for metastatic melanoma were used in PHAROS study.

RCT COLUMBUS part 1 and 2 compared encorafenib 450 mg once daily plus binimetinib 45 mg twice a day (COMBO450), encorafenib 300 mg once daily (ENCO300), and 960 mg vemurafenib arms as well as encorafenib 300 mg once daily plus binimetinib 45 mg twice daily (COMBO300) in patients with

BRAFV600-mutated unresectable or metastatic melanoma. For the scope of this WSP no new dose-response studies in the new indication have been performed.

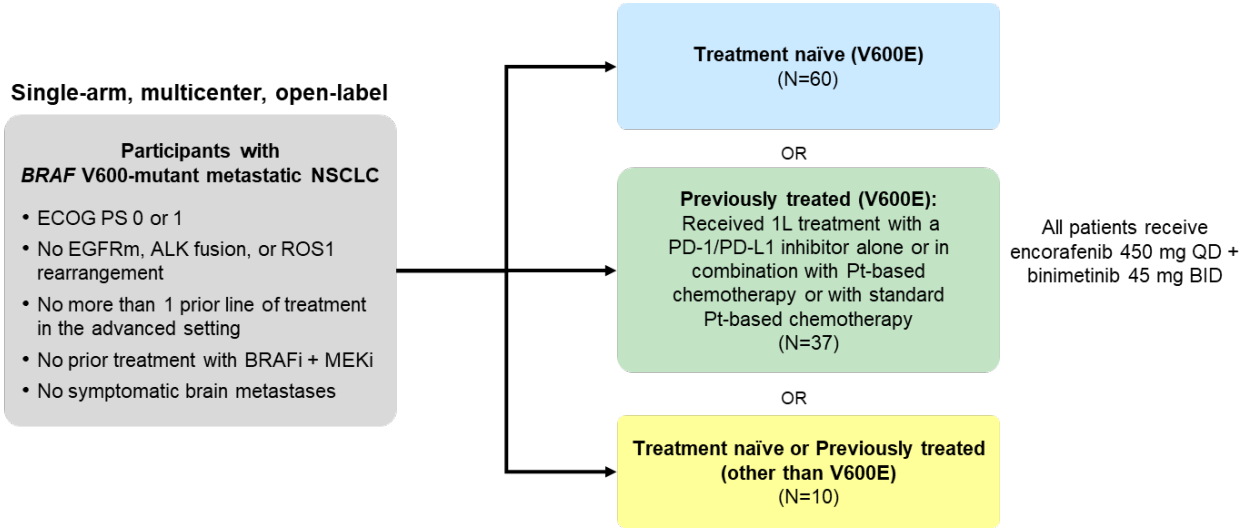
2.4.2. Main study

PHAROS, A Phase 2, Open-label Study of Encorafenib + Binimetinib in Patients with BRAF V600-mutant Non-Small Cell Lung Cancer (PfizerC4221008/ARRAY-818-202, EudraCT Number 2019-000417-37, NCT03915951)

Methods

PHAROS is the single efficacy study without a control group pertinent to the claimed indication. It is an open label multicentre, multinational (56 sites in 5 countries) single arm trial investigating two cohorts (treatment-naïve and previously treated patients with NSCLC).

Figure 13: PHAROS Participants



Study participants

The table below summarizes in- and exclusion criteria of the protocol (version 5.0).

Table 15: Key Patient Eligibility Criteria in PHAROS Study Pertaining to Efficacy

Key Eligibility Criteria - Protocol Version 5.0
Gender and age
Male or female aged ≥ 18 years
Diagnosis
• Histologically confirmed NSCLC that was currently Stage IV (M1a M1b, M1c- AJCC 8th edition) • Evidence of measurable disease per RECIST v1.1 • Exclusion of participants with symptomatic brain metastasis, leptomeningeal disease, or other active CNS metastases
Mutation status
• Presence of *BRAF* V600E mutation in tumour tissue previously determined by a local laboratory assay

Key Eligibility Criteria - Protocol Version 5.0
• Exclusion of participants with EGFR mutation, ALK fusion oncogene, or ROS1 rearrangement • Able to provide a representative tumour specimen for confirmatory mutation status testing
Prior treatment
• Either treatment-naïve (e.g., no prior systemic therapy for advanced/metastatic disease), OR who had received 1) first-line platinum-based chemotherapy OR 2) first-line treatment with an anti-PD-1/PD-L1 inhibitor given alone, or in combination with platinum-based chemotherapy, or in combination with immunotherapy (e.g., ipilimumab) with or without platinum-based chemotherapy • No prior treatment with any BRAF inhibitor (e.g., dabrafenib, vemurafenib, XL281/BMS-908662, etc), or any MEKi (e.g., trametinib, cobimetinib, selumetinib, RDEA119, etc) • Sufficient interval between prior chemotherapy or biologic therapy and start of study treatment
Baseline health status
• ECOG PS of 0 or 1
Medical history
• No concurrent or previous other malignancy within 2 years of study entry, except curatively treated basal or squamous cell skin cancer, prostate intraepithelial neoplasm, carcinoma in-situ of the cervix, Bowen's disease and Gleason ≤ 6 prostate cancer. • No history or current evidence of impairment of gastrointestinal function or disease which may significantly alter the absorption of oral study treatment, no history of thromboembolic or cerebrovascular events ≤ 12 weeks prior to the first dose of study treatment**,** no impaired cardiovascular function or clinically significant cardiovascular diseases.
Concomitant medication
• No prior treatment with a non-topical medication known to be a strong inhibitor of CYP3A4 in the 7 days prior to starting study treatment

BRAF: B-Raf proto-oncogene, serine/threonine kinase; CYP3A4: cytochrome P450 3A4; ECOG PS: Eastern Cooperative Oncology Group performance status; mNSCLC: metastatic non-small cell cancer; MEK: mitogen-activated protein kinase; RAS: rat sarcoma viral oncogene homologue; RECIST: Response Evaluation Criteria in Solid Tumours;

Concerning the BRAF mutation status (V600E [or V600K/D respectively]) the protocol mentions that a local laboratory assay of the BRAF mutation in tumour tissue or blood (e.g., ctDNA genetic testing) is required (inclusion criterion 4). Inclusion criteria 5 requires, in addition, that the investigator must obtain, prior to enrolment, adequate tumour tissue for submission to a central laboratory for confirmation of BRAFV600 mutation status. Of note, besides tissue ("*1 block or a minimum of 8 unstained slides of analysable tissue*") also pleural fluid (not liquid but as formalin-fixed, paraffin-embedded block) was also permitted for the scope of central analysis of mutation status.

By protocol (inclusion criterion 4) PHAROS had the option (besides naïve and pre-treated patients) to investigate a third cohort, i.e. patients with a BRAF V600K or V600D mutation. In terms of results, however, no patient was enrolled in this "cohort" with other mutation than V600E.

Treatments

Study treatment was COMBO 450 (the combination of encorafenib 450 mg QD and binimetinib 45 mg BID) as detailed below in Table 16 of the protocol. In terms of protocol, study treatment was administered in cycles ("*Treatment will be administered in 28-day (± 3 days) cycles*"). Ultimately it was, however, a continuous administration (with an expected study treatment duration of 12 to 18 months) during the entire conduct of the study.

Table 16: Study treatment

Study Treatment Name	Encorafenib	Binimetinib
Dose Formulation	Capsule	Tablet
Unit Dose Strength	75 mg	15 mg
Dosage Levels	450 mg QD	45 mg BID
Route of Administration	Oral	Oral
Sourcing	Encorafenib will be provided centrally by the Sponsor or designee	Binimetinib will be provided centrally by the Sponsor or designee
Packaging and Labeling	Encorafenib will be provided in high-density polyethylene bottles. Each bottle will be labeled per local regulatory requirements.	Binimetinib will be provided in high-density polyethylene bottles. Each bottle will be labeled per local regulatory requirements.
Former Names or Aliases	LGX818 ONO-7702 W0090	ARRAY-438162 MEK162 ONO-7703 W0074

Patients may continue to receive study treatment until they meet any of the protocol defined criteria for treatment withdrawal (including progression and death). If the patient discontinues study treatment, then the treatment period will end, and the patient will enter the follow-up period for safety, disease assessments (if applicable), subsequent anticancer therapies, and survival.

Table 17: Dose Reductions for Encorafenib

Dose Level	Encorafenib
0 (starting dose)	450 mg QD
-1	300 mg QD
-2	225 mg[a] QD

NOTE: Dose reduction should be based on the highest AE grade.
a Dose reduction below 225 mg QD of encorafenib is not allowed.

Objectives

The primary objective of PHAROS was:

- To evaluate the efficacy of encorafenib + binimetinib in treatment-naïve and previously treated patients with BRAFV600E-mutant NSCLC as measured by ORR (see endpoints below).

Secondary objectives were:

- To evaluate the efficacy of encorafenib + binimetinib in treatment-naïve and previously treated patients with BRAFV600E-mutant NSCLC as measured by DOR, DCR, PFS, and TTR (see endpoints below).
- To evaluate the efficacy of encorafenib + binimetinib in treatment-naïve and previously treated patients with BRAFV600E-mutant NSCLC with respect to OS
- To evaluate the safety and tolerability of encorafenib + binimetinib in treatment-naïve and previously treated patients with BRAFV600E-mutant NSCLC

Exploratory objectives were:

- To evaluate the PK of encorafenib and its metabolite LHY746 and binimetinib in in patients with BRAFV600-mutant NSCLC
- To assess blood ctDNA mutation status

Outcomes/endpoints

The primary endpoints (by cohort) were defined as:

- ORR defined as the proportion of patients who have achieved a confirmed best overall response (CR or PR) as determined by IRR (independent radiological review) per RECIST v1.1 in the treatment-naïve setting
- ORR defined as the proportion of patients who have achieved a confirmed best overall response (CR or PR) as determined by IRR per RECIST v1.1 in the previously treated setting.

Secondary endpoints were defined as:

- Confirmed ORR by Investigator per RECIST v1.1
- DOR (by IRR and by Investigator) defined as the time from the date of the first documented response (CR or PR) that is subsequently confirmed (by IRR and by Investigator, respectively) to the earliest date of disease progression, per RECIST v1.1, or death due to any cause
- DCR (by IRR and by Investigator), defined as the proportion of patients who have a confirmed CR or confirmed PR, or SD per RECIST v1.1
- PFS (by IRR and by Investigator), defined as the time from the date of first dose of study drug to the earliest date of disease progression, per RECIST v1.1, or death due to any cause
- TTR (by IRR and Investigator), defined as the time from the date of first dose to the first documentation of objective response (CR or PR) which is subsequently confirmed (by IRR and by Investigator, respectively)
- OS defined as the time from the date of first dose of study drug to the date of death due to any cause
- Incidence and severity of AEs graded according to the NCI CTCAE v4.03 and changes in clinical laboratory parameters, vital signs, ECGs and ECHO/MUGA scans

Exploratory endpoints were defined as:

- Plasma concentration-time profiles and PK parameter estimates for encorafenib and its metabolite LHY746 and binimetinib
- Genomic analysis of ctDNA in blood samples

Concerning the number of two (primary) analyses (by "cohort") of the primary endpoint ORR in a SAT it should be noted that the term 'cohort' is used neither in the protocols nor the statistical analysis plan (SAP). "Cohorts" is a term used in deriving documents such as CO and CSE (Clinical Summary of Efficacy). The figure below exemplifies those 3 analyses of the primary endpoints by three (potential) 'cohorts'.

Sample size

Following the SAP, the sample size calculation was based on the primary endpoint ORR as determined by IRR per RECIST v1.1 whereas the hypotheses to be tested were described in Section 4.2 of the SAP. The referring hypotheses are provided below:

> *The study is designed to test the null hypothesis of ORR ≤ 39% for **treatment-naïve** participants with BRAFV600E NSCLC, which is considered not sufficiently clinically meaningful to warrant further study on encorafenib and binimetinib in this indication where similar therapies are already available. The alternative hypothesis is ORR >39% with the assumption that the true ORR is ≥ 65%. Hypotheses are based on the results observed in the dabrafenib plus trametinib study in BRAFV600E-mutant NSCLC participants, in which the ORR per investigator assessment was 64% (95% CI: 46, 79) for treatment-naïve participants (Planchard et al 2017[5]), and the results observed in participants with NSCLC whose tumours expressed PD-L1 levels with a TPS ≥ 50% and received pembrolizumab as a single agent (Keynote-042) in which ORR per IRR was 39% (95% CI: 34, 45) (Mok et al 2019[4]).*
>
> *For previously treated participants with BRAFV600E NSCLC, the null hypothesis of ORR ≤ 20% will be tested. The alternative hypothesis is ORR >20% with the assumption that the true ORR is ≥ 45%. This hypothesis is based on the ORR of 18% (95% CI: 14, 23) observed in previously treated participants with NSCLC whose tumours expressed PD-L1 levels with a TPS ≥ 1% and who received pembrolizumab as a single agent (Keynote-010; Herbst et al 2016[2]).*

Accordingly, the sample size was estimated to be no more than 107 NSCLC patients with any BRAF V600 mutation (at least 60 treatment-naïve and 37 previously treated.

PHAROS had 3 secondary efficacy objectives and, accordingly 6 secondary endpoints as follows:

- Confirmed ORR by Investigator per RECIST v1.1
- DOR (by IRR and by Investigator) defined as the time from the date of the first documented response (CR or PR) that is subsequently confirmed (by IRR and by Investigator, respectively) to the earliest date of disease progression, per RECIST v1.1, or death due to any cause
- DCR (by IRR and by Investigator), defined as the proportion of patients who have a confirmed CR or confirmed PR, or SD per RECIST v1.1
- PFS (by IRR and by Investigator), defined as the time from the date of first dose of study drug to the earliest date of disease progression, per RECIST v1.1, or death due to any cause
- TTR (by IRR and Investigator), defined as the time from the date of first dose to the first documentation of objective response (CR or PR) which is subsequently confirmed (by IRR and by Investigator, respectively)
- OS defined as the time from the date of first dose of study drug to the date of death due to any cause

Randomisation

Not applicable.

Blinding (masking)

PHAROS is an open label, thus, not blinded study.

Statistical methods

The analysis populations are defined as shown in the below table.

Table 18: Analysis Sets Defined for the Study

Analysis Set	Description	Analysis Set Applies to Following Endpoints
Screened	All participants who signed the ICD.	
SS	All participants who received at least 1 dose of study treatment.	Safety/Efficacy
PK	All participants in the SS who had at least 1 post dose PK blood collection with associated bioanalytical results after the first dose of study treatment.	PK

The Safety Analysis Set (SS) was the primary population for the analysis of all efficacy endpoints. Data were summarized for treatment-naïve participants, previously treated participants, and overall.

The ORR by IRR (primary) and investigator (sensitivity analysis) were calculated with the exact 2-sided Clopper-Pearson 95% CI. Statistical hypotheses were defined as described in the sample size calculation above.

For time to event endpoints (DOR, PFS, OS), an estimate of the survival functions was constructed using the KM method.

DOR was calculated for participants who have achieved a confirmed response (i.e., CR or PR). If a participant with a CR or PR has neither progressed nor died at the time of the analysis cut-off or at the start of any new anticancer therapy, the participant was censored at the date of last adequate tumours assessment. The same rules used for censoring of PFS were applied. The censoring and event date options to be considered for the PFS analysis are presented in the table below.

Table 19: PFS Outcome and Event Dates

Situation	**Date of Progression/Censoring**	**Outcome**
No adequate baseline assessment	Date of treatment start date [a]	Censored [a]
PD or death ≤ 16 (or 24) [b] weeks after last adequate tumor assessment or ≤ 16 weeks after treatment start date	Date of PD or death	Event
PD or death > 16 (or 24) [b] weeks after the last adequate tumor assessment [c]	Date of last adequate tumor assessment [c] documenting no PD prior to new anticancer therapy or missed assessments	Censored
No PD		
New anticancer therapy given		

a If the participant dies ≤16 weeks after treatment start date, the death is an event with date on death date.

b Durations are equal to 2 times the length of the tumor assessment interval, which is 16 weeks for the first 12 months after treatment start date, and 24 weeks thereafter.

c If there are no adequate post-baseline assessments prior to the PD or death, then the time without adequate assessment should be measured from treatment start date; if the criteria is met, the censoring will be on treatment start date.

Time to response was calculated for the subgroup of participants with a confirmed objective tumour response. TTR was summarized using descriptive statistics.

According to protocol, the Sponsor may conduct 2 interim analyses for treatment-naïve patients, after about 90% [n=54] of the planned treatment-naïve patients [n=60] will be enrolled and after 6 months from the last treatment-naïve patient enrolled into the study. Results of the IA were considered for discussion, based on criteria specified in the SAP, with regulatory authorities.

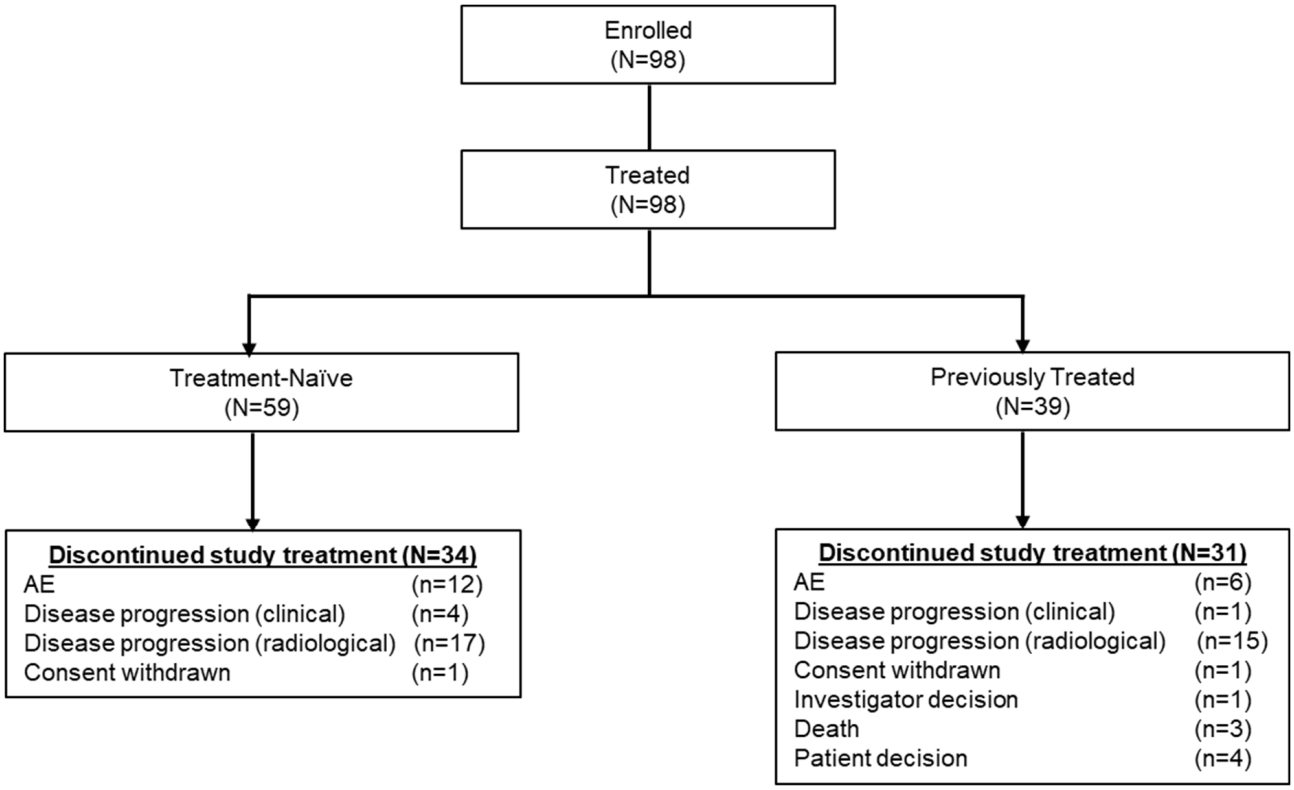
An interim analysis was performed after 58 treatment-naïve participants were enrolled and treated. Following regulatory interactions based upon the interim analysis results, it was decided to continue the study as is in order to collect further follow-up data for responding treatment-naïve participants. Thus, the interim analysis results are not reported in this CSR. The second IA was removed in the SAP.

For duration of response, patients were censored at start of new anticancer therapy. Additional analyses were provided where (i) these patients are not censored (if these were continued to be followed after start of new anti-cancer therapy), and (ii) new anticancer therapy is considered as an event. In addition, analyses were provided where patients with PD or death > 16 (or 24) weeks after the last adequate tumour assessment are not censored.

Results

Participant flow

Figure 14: Participant flow (DCO 22 Sept 2022)



Patient Disposition

As of the primary completion date (PCD) of 22 September 2022, corresponding to 14 months after the last participant enrolled in the treatment-naïve cohort, 33 (33.7%) participants were continuing to receive study treatment, of these 25 (42.4%) participants were treatment-naïve and 8 (20.5%) participants were previously treated.

As of 19 July 2023, 23 (23.5%) participants were continuing to receive study treatment, of these 19 (32.2%) participants were treatment-naïve and 4 (10.3%) participants were previously treated. Since the PCD of 22 September 2022, 10 participants discontinued study treatment (6 treatment naïve and 4 previously treated).

Overall, at the COD of 19 July 2023, 26 (26.5%) participants had permanently discontinued study treatment but continued to be followed up for disease progression or survival and 49 (50.0%) had discontinued the study.

Table 20: Patient Disposition (Safety set, COD of 19July 2023)

	Encorafenib + Binimetinib		
Disposition Reason	Treatment Naive N=59 n (%)	Previously Treated N=39 n (%)	Total N=98 n (%)
Pts treated	59 (100)	39 (100)	98 (100)
Treatment discontinued	40 (67.8)	35 (89.7)	75 (76.5)
Treatment ongoing[a]	19 (32.2)	4 (10.3)	23 (23.5)
Primary reason for treatment discontinuation			
Adverse event	14 (23.7)	6 (15.4)	20 (20.4)
Disease progression (clinical)	5 (8.5)	1 (2.6)	6 (6.1)
Disease progression (radiological)	18 (30.5)	19 (48.7)	37 (37.8)
Consent withdrawn	1 (1.7)	1 (2.6)	2 (2.0)
Investigator decision	1 (1.7)	1 (2.6)	2 (2.0)
Death	0	3 (7.7)	3 (3.1)
Patient decision	0	4 (10.3)	4 (4.1)
Other	1 (1.7)	0	1 (1.0)
Study evaluation after treatment discontinuation			
Pts who continued to be followed for disease or survival	15 (25.4)	11 (28.2)	26 (26.5)
Pts who discontinued the study	25 (42.4)	24 (61.5)	49 (50.0)
Primary reason for study discontinuation			
Withdrawal of consent	2 (3.4)	5 (12.8)	7 (7.1)
Lost to follow-up	2 (3.4)	1 (2.6)	3 (3.1)
Death	21 (35.6)	17 (43.6)	38 (38.8)
Other	0	1 (2.6)	1 (1.0)

Source Listing:
[a] Participants ongoing at the time of the data cutoff.

Recruitment

Study dates as of the CSR version 2.0 as of 11 May 2023 (final CSR version 1.0 was dated on 02 December 2022) are as follows:

Study Initiation Date	04 June 2019
Primary Completion Date:	22 September 2022
Data Cut-off Date:	22 September 2022
Updated efficacy analysis DCO:	19 July 2023

A total of 98 participants were enrolled and received at least one dose of study treatment: 59 were treatment-naïve and 39 were previously treated.

The number of treatment-naïve participants (N = 59) was less than specified in the protocol (N = 60) as following closure of enrolment of the treatment-naïve participants, one participant initially categorised as treatment-naïve was re-categorised to previously treated after it was determined that they had received prior treatment for metastatic disease.

Prospective sample size considerations estimated an overall minimum of 97 and a maximum of 107 patients to be recruited (and treated). With actually 98 patients enrolled (and treated), by result the number investigated in PHAROS is in the prospective planned range for the overall (naïve/not entirely naïve, i.e. overall BRAFi_MEKi naïve) population. Recruitment details by "cohort" are presented above.

Conduct of the study

The phase 2 study (PHAROS) was conducted in a molecularly well-defined subset of participants with metastatic NSCLC with BRAF V600E mutation according to local testing [all but five treatment-naïve participants in PHAROS study had V600E mutation centrally confirmed]. The five countries involved, following the listing of 56 sites, were Italy, Korea (Republic), the Netherlands, Spain, and the United States (of America).Dates of the protocol and its amendments were:

Version 0:	27 November 2018
Version 1:	04 March 2019
Version 2:	03 October 2019
Version 3:	25 August 2020
Version 4:	16 February 2021
Version 5:	24 September 2021

Amendment 1 modified the inclusion criterion for patients with moderate hepatic impairment as per binimetinib labelling recommendations.

Amendment 2 revised patient eligibility criteria based on investigator feedback and changes in standard of care for identifying BRAF mutation status in this patient population.

Amendment 3 increased the sample size to support a potential registrational status of the study, and to provide clarification on acceptable methods for BRAF mutation status confirmation.

Amendment 4 revised the primary objective and corresponding endpoint into 2 subgroups (treatment-naïve and previously treated) and updated the sample size to describe the 2 subgroups in order to support a registrational status of the study. Corresponding statistical analyses sections were updated to reflect these changes.

Amendment 5 was to provide clarification to the eligibility for the previously treated patients, and to update the Secondary Objectives and Interim Analysis sections to maintain consistency with the SAP.

At least 1 significant protocol deviation was reported in 83 (84.7%) participants (Table 21).

The most frequent (≥25% of participants) significant protocol deviations were in the categories of study procedures/assessments (62.2%) and study treatment compliance (42.9%).

Table 21: Significant Protocol Deviations (SS)

	Encorafenib + Binimetinib		
Protocol Deviation	Treatment Naive N=59 n (%)	Previously Treated N=39 n (%)	Total N=98 n (%)
Any Significant Protocol Deviation	52 (88.1)	31 (79.5)	83 (84.7)
Data Privacy	6 (10.2)	2 (5.1)	8 (8.2)
Exclusion Criteria	1 (1.7)	1 (2.6)	2 (2.0)
ICF Process/Timing	12 (20.3)	4 (10.3)	16 (16.3)
Inclusion Criteria	3 (5.1)	0	3 (3.1)
Investigator Record Keeping	2 (3.4)	0	2 (2.0)
Investigator Safety Reporting	6 (10.2)	4 (10.3)	10 (10.2)
Missing Endpoint Assessments	3 (5.1)	0	3 (3.1)
Other Protocol Deviation	1 (1.7)	0	1 (1.0)
Study Procedures/Assessments	42 (71.2)	19 (48.7)	61 (62.2)
Study Treatment Administration/Dispense Error	8 (13.6)	1 (2.6)	9 (9.2)
Study Treatment Compliance	28 (47.5)	14 (35.9)	42 (42.9)
Study Treatment Supplies/Control	1 (1.7)	0	1 (1.0)
Visit Scheduling	12 (20.3)	3 (7.7)	15 (15.3)
Withdrawal/Termination Criteria	1 (1.7)	0	1 (1.0)

Baseline data

The baseline data are provided by "cohorts" (not stated in the table) in the following table:

Table 22: PHAROS: Demographics (Full Analysis Set)

	Encorafenib + Binimetinib		
	Treatment-Naïve N=59	Previously Treated N=39	Total N=98
Age (years)			
N	59	39	98
Mean	66.5	69.7	67.8
SD	8.50	9.13	8.85
Median	68.0	71.0	69.5
Minimum	47	53	47
Maximum	83	86	86
Age category, n (%)			
<65	23 (39.0)	13 (33.3)	36 (36.7)
≥65	36 (61.0)	26 (66.7)	62 (63.3)
Sex, n (%)			
Female	33 (55.9)	19 (48.7)	52 (53.1)
Male	26 (44.1)	20 (51.3)	46 (46.9)
Race, n (%)			
Asian	3 (5.1)	4 (10.3)	7 (7.1)
White	53 (89.8)	33 (84.6)	86 (87.8)
Other	2 (3.3)	2 (5.1)	4 (4.1)
Unknown	1 (1.7)	0	1 (1.0)
Ethnicity, n (%)			
Not Hispanic/Latino	58 (98.3)	39 (100)	97 (99.0)
Unknown	1 (1.7)	0	1 (1.0)

	Encorafenib + Binimetinib		
	Treatment-Naïve N=59	Previously Treated N=39	Total N=98
Weight (kg, at baseline)			
N	59	39	98
Mean	74.64	72.14	73.64
SD	23.129	14.443	20.077
Median	70.00	73.20	72.45
Minimum	39.8	48.3	39.8
Maximum	143.7	115.8	143.7
Height (cm, at screening)			
N	58	38	96
Mean	167.11	167.35	167.21
SD	11.742	9.908	10.999
Median	165.10	166.00	165.55
Minimum	143.0	151.1	143.0
Maximum	210.5	193.0	210.5
ECOG performance status, n (%)			
0	19 (32.2)	7 (17.9)	26 (26.5)
1	40 (67.8)	32 (82.1)	72 (73.5)
Smoking status			
Current	8 (13.6)	5 (12.8)	13 (13.3)
Former	33 (55.9)	23 (59.0)	56 (57.1)
Never	18 (30.5)	11 (28.2)	29 (29.6)

Source PHAROS CSR, Listing 16.2.4.1.1

Table 23 below provides an overview on baseline disease characteristics whereas Table 24 below provides further insights in the prior (anticancer) treatment.

Table 23: PHAROS: Baseline Disease Characteristics (Full Analysis Set)

	Encorafenib + Binimetinib		
	Treatment-Naïve N=59	Previously Treated N=39	Total N=98
Time from initial diagnosis to start of study treatment (months)			
N	59	39	98
Mean	10.15	22.39	15.02
SD	22.790	23.353	23.674
Median	1.77	11.76	3.35
Minimum	0.5	1.2	0.5
Maximum	122.8	86.6	122.8
TNM (AJCC Staging) at study entry, n (%)			
IV	20 (33.9)	19 (48.7)	39 (39.8)
IV-A	25 (42.4)	7 (17.9)	32 (32.7)
IV-B	14 (23.7)	13 (33.3)	27 (27.6)
Tumour Histology, n (%)			
Adenocarcinoma	57 (96.6)	38 (97.4)	95 (96.9)
Squamous Cell Carcinoma	1 (1.7)	1 (2.6)	2 (2.0)
Other	1 (1.7)	0	1 (1.0)
Brain Metastases, n (%)			
Yes	4 (6.8)	4 (10.3)	8 (8.2)
No	55 (93.2)	35 (89.7)	90 (91.8)

Source PHAROS CSR,

Table 24: PHAROS: Prior systemic therapy (Safety Set)

	Encorafenib + Binimetinib		
	Treatment-Naïve N=59	Previously Treated N=39	Total N=98
Number of pts with at least one prior systemic treatment, n (%)	4 (6.8)	39 (100)	43 (43.9)
Having received prior immunotherapy	0	24 (61.5)	24 (24.5)
Immunotherapy only		11(28.2)	
Immunotherapy and Chemotherapy (in combination or sequentially)		13(33.3)	
Without prior immunotherapy		15(38.5)	
Chemotherapy without immunotherapy	4 (6.8)	15(38.5)	19 (19.4)
Received at least one regimen of TKI	0	0	0
Total number of regimens, n (%)			
1	2 (3.4)	33 (84.6)	35 (35.7)
2	2 (3.4)	5 (12.8)	7 (7.1)
3	0	1 (2.6)	1 (1.0)
Total number of regimens			
N	4	39	43
Mean	1.5	1.2	1.2
SD	0.58	0.45	0.47
Median	1.5	1.0	1.0
Minimum	1	1	1
Maximum	2	3	3
Setting at last medicationa, n (%)			
Neoadjuvant	1 (1.7)	0	1 (1.0)
Adjuvant	3 (5.1)	0	3 (3.1)
Metastatic	0	29 (74.4)	29 (29.6)
Maintenance	0	3 (7.7)	3 (3.1)
Locally Advanced	0	3 (7.7)	3 (3.1)
Palliative	0	4 (10.3)	4 (4.1)
Other	0	0	0

Source PHAROS CSR,
[a] The last medication is defined based on the last end date of all prior regimen components.

In terms of baseline disease characteristic, nearly all patients had, by histology, an adenomatous NSCLC, one had a squamous (non-small cell LC). TNM (AJCC Staging) stage was at least IV comprising as metastasis, however, few brain metastases only (8.2% of n=98 = 8 patients had brain metastases defining AJCC stage IV).

Of note, 4 treatment naïve patients had prior systemic chemotherapy. All had received adjuvant chemotherapy. In the previously treated population 15 patient "only" (15 of 39) had chemotherapy without immunotherapy - but the majority of this sub-population (61.5%) had immunotherapy (among others immunotherapy and chemotherapy [in combination or sequentially]).

Numbers analysed

Safety set and intention-to-treat set are identical by result, i.e. 98 patients.

Two analysis sub-populations ("cohorts") consisting in 59 (so called "naïve") and 38 (so called "previously treated") patients were introduced not later than protocol amendment 4.

Outcomes and estimation

The PHAROS trial had two different null hypotheses for ORR, discerned by "treatment setting".

Unless otherwise specified, analyses are presented per primary completion date (PCD) of 22 September 2022.

Primary efficacy endpoint - ORR

Table 25: Best Overall Response by IRR, per RECIST v1.1 (Safety Set) (DCO 22 Sept 2022)

	Encorafenib + Binimetinib		
	Treatment Naïve N=59 n (%)	Previously Treated N=39 n (%)	Total N=98 n (%)
Best overall response (based on confirmed response)[a]			
Complete response (CR)	9 (15.3)	4 (10.3)	13 (13.3)
Partial response (PR)	35 (59.3)	14 (35.9)	49 (50.0)
Stable disease	10 (16.9)	13 (33.3)	23 (23.5)
Progressive disease (PD)	2 (3.4)	3 (7.7)	5 (5.1)
Not evaluable (NE)	3 (5.1)	5 (12.8)	8 (8.2)
Number of pts with best overall response non-evaluable[b]			
- No post-baseline assessments due to early death (defined- as death prior to 6 weeks after date of first dose)	0	2 (40.0)	2 (25.0)
- No post-baseline assessments due to other reason	1 (33.3)	2 (40.0)	3 (37.5)
- Stable disease occurred < 6 weeks after the start of treatment and no subsequent tumour assessments	2 (66.7)	1. (20.0)	3 (37.5)
Objective response rate (confirmed) (ORR: CR+PR)	44 (74.6)	18 (46.2)	62 (63.3)
95% CI[c]	(61.6 - 85.0)	(30.1 - 62.8)	(52.9 - 72.8)

[a] Best overall response is based on IRR using RECIST v1.1
[b] The denominator of subcategories is the total number of participants with best overall response=Not evaluable (NE) according to RECIST v1.1 per IRR.
[c] Estimated 95% CIs for ORR were obtained using the exact Clopper-Pearson method.

Secondary endpoints

Confirmed ORR by Investigator per RECIST v1.1

Confirmed ORR by investigator in the overall population was **54.1%** (3 CRs and 50 PRs; 53/98=0.541;).

Treatment-naïve participants: The ORR was **62.7%** (95% CI: 49.1, 75.0), including 2 (3.4%) CRs and 35 (59.3%) PRs.

Previously treated participants: The ORR was **41.0%** (95% CI: 25.6, 57.9), including 1 (2.5%) CR and 15 (38.5%).

A summary of the concordance between IRR and Investigator assessments of confirmed objective response (SS) is provided in **Table 26.**

Table 26: Summary of Agreement and Disagreement Between Response Results Based on Derived Investigator Assessment and IRR (Safety Set) (DCO 22 Sept 2022)

	Encorafenib + Binimetinib		
	Treatment-Naïve N=59	Previously Treated N=39	Total N=98
No. of Discrepancy (%)			
IRR Response/Investigator No Response	9 (15.3)	4 (10.3)	13 (13.3)
IRR No Response/Investigator Response	2 (3.4)	2 (5.1)	4 (4.1)
Total Event Disagreement Rate [a]	11 (18.6)	6 (15.4)	17 (17.3)
No. of Agreement (%)			
IRR Response/Investigator Response	35 (59.3)	14 (35.9)	49 (50.0)
IRR No Response/Investigator No Response	13 (22.0)	19 (48.7)	32 (32.7)
Total Event Agreement Rate [b]	48 (81.4)	33 (84.6)	81 (82.7)

Note: Response refers to confirmed CR or PR.
[a] The total event disagreement rate measures the proportion of participants for whom there is a discrepancy between the IRR and investigator.

[b] The total event agreement rate measures the proportion of participants for whom there is a concordance between the IRR and investigator.

Duration of response

Table 27: Duration of Response per RECIST v1.1 According to IRR (SS, Confirmed Responders) (DCO 22 Sept 2022)

	Encorafenib+Binimetinib		
	Treatment-Naïve N=44	Previously Treated N=18	Total N=62
Number of pts with confirmed response, n (%)	44 (100)	18 (100)	62 (100)
Number of events, n (%)	12 (27.3)	6 (33.3)	18 (29.0)
Progression	11 (25.0)	5 (27.8)	16 (25.8)
Death due to any cause	1 (2.3)	1 (5.6)	2 (3.2)
Number of censored, n (%)	32 (72.7)	12 (66.7)	44 (71.0)
Percentiles of duration of response (months) (95% CI)[a]			
25th	14.0 (4.5, NE)	7.4 (4.4, NE)	12.0 (6.3, NE)
50th	NE (23.1, NE)	16.7 (7.4, NE)	NE (16.7, NE)
75th	NE (NE, NE)	NE (16.7, NE)	NE (NE, NE)
Duration of response (months), n (%)			
<3	3 (6.8)	1 (5.6)	4 (6.5)
≥3	41 (93.2)	17 (94.4)	58 (93.5)
≥6	33 (75.0)	12 (66.7)	45 (72.6)
≥9	31 (70.5)	10 (55.6)	41 (66.1)
≥12	26 (59.1)	6 (33.3)	32 (51.6)
≥24	7 (15.9)	3 (16.7)	10 (16.1)

[a] Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

Table 28: Duration of Response per RECIST v1.1 According to IRR (Safety Set, Confirmed Responders, DCO 19 July 2023)

	Encorafenib + Binimetinib		
	Treatment Naive N=44	Previously Treated N=18	Total N=62
Number of pts with confirmed response, n (%)	44 (100)	18 (100)	62 (100)
Number of events, n (%)	17 (38.6)	8 (44.4)	25 (40.3)
Progression	16 (36.4)	7 (38.9)	23 (37.1)
Death due to any cause	1 (2.3)	1 (5.6)	2 (3.2)
Number of censored, n (%)	27 (61.4)	10 (55.6)	37 (59.7)
Percentiles of duration of response (months) (95% CI)[a]			
25th	14.0 (4.5, 23.2)	7.4 (4.4, 16.7)	12.0 (6.3, 20.4)
50th	40.0 (23.1, NE)	16.7 (7.4, NE)	40.0 (16.7, NE)
75th	NE (40.0, NE)	NE (16.7, NE)	NE (40.0, NE)
Duration of response (months), n (%)			
<3	3 (6.8)	0	3 (4.8)
≥3	41 (93.2)	18 (100)	59 (95.2)
≥6	33 (75.0)	13 (72.2)	46 (74.2)
≥9	31 (70.5)	11 (61.1)	42 (67.7)
≥12	28 (63.6)	8 (44.4)	36 (58.1)
≥24	13 (29.5)	4 (22.2)	17 (27.4)

Source Listing: Listing 16.2.6.5
[a] Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

DCR (by IRR and by Investigator)

DCR (disease control rates) according to IRR and investigator assessment are presented in Table 29.

Table 29: Disease Control rate per RECIST v1.1 (Safety Analysis Set) (DCO 22 Sept 2022)

	Encorafenib + Binimetinib					
	Treatment-Naïve (N=59)		**Previously Treated (N=39)**		**Total (N=98)**	
Subgroup	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
IRR						
DCR at 24 weeks	38 (64.4)	(50.9, 76.4)	16 (41.0)	(25.6, 57.9)	54 (55.1)	(44.7, 65.2)
DCR at 48 weeks	30 (50.8)	(37.5, 64.1)	10 (25.6)	(13.0, 42.1)	40 (40.8)	(31.0, 51.2)
Derived Investigator Assessment						
DCR at 24 weeks	40 (67.8)	(54.4, 79.4)	19 (48.7)	(32.4, 65.2)	59 (60.2)	(49.8, 70.0)
DCR at 48 weeks	32 (54.2)	(40.8, 67.3)	9 (23.1)	(11.1, 39.3)	41 (41.8)	(31.9, 52.2)

Source ADaM ADEFF, ADaM ADEFFC, ADaM ADSL – Data Cut-off 22SEP2022
DCR = Disease Control Rate (Confirmed CR + Confirmed PR + Stable Disease)
Note: Estimated 95% Cis for ORR was obtained using the exact Clopper-Pearson method.

PFS (by IRR and by Investigator)

PFS by IRR is summarized in Table 30 and Figure 15. Updated PFS analysis is summarised in Table 31 and Figure 16.

Table 30: Progression-Free Survival per RECIST v1.1 According to IRR (Safety Analysis Set) (DCO 22 Sept 2022)

	Encorafenib+Binimetinib		
	Treatment-Naïve N=59	Previously Treated N=39	Total N=98
Number of PFS events, n (%)	21 (35.6)	17 (43.6)	38 (38.8)
Progression	18 (30.5)	12 (30.8)	30 (30.6)
Death without progression	3 (5.1)	5 (12.8)	8 (8.2)
Number of censored, n (%)	38 (64.4)	22 (56.4)	60 (61.2)
No adequate baseline assessment	0	0	0
Start of new anticancer therapy	11 (18.6)	6 (15.4)	17 (17.3)
Event after missing or inadequate assessments	1 (1.7)	1 (2.6)	2 (2.0)
Withdrawal of consent	1 (1.7)	4 (10.3)	5 (5.1)
Lost to follow-up	0	0	0
No adequate postbaseline tumour assessment	0	1 (2.6)	1 (1.0)
Ongoing without an event	25 (42.4)	10 (25.6)	35 (35.7)
Kaplan-Meier Estimates of Time to Event (Months) Percentiles (95% CI) [a]			
25th	6.0 (4.6, 19.5)	5.4 (1.9,9.0)	5.6 (3.7, 9.2)
50th	NE (15.7, NE)	9.3 (6.2, NE)	24.8 (13.7, NE)
75th	NE (NE, NE)	NE (13.8, NE)	NE (NE, NE)

Source PHAROS CSR,

[a] Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

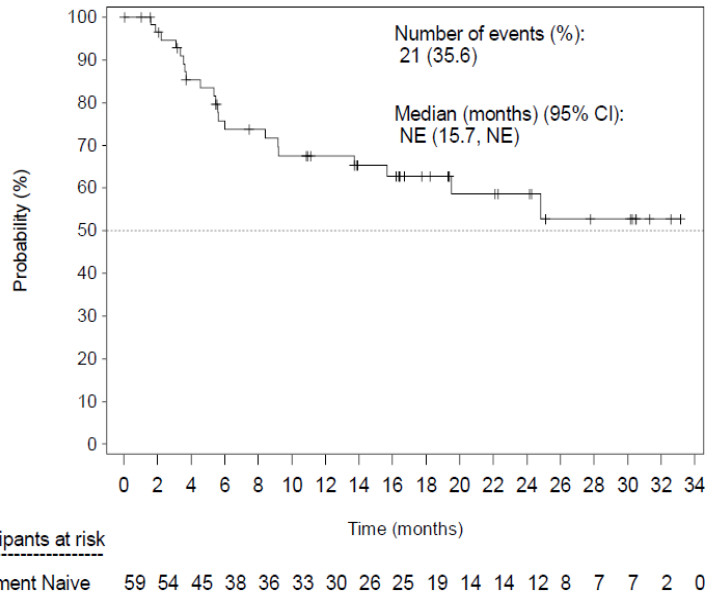
Table 31: Progression-Free Survival per RECIST v1.1 According to IRR (Safety Analysis Set, COD of 19 July 2023)

	Encorafenib+Binimetinib		
	Treatment-Naïve N=59	Previously Treated N=39	Total N=98
Number of PFS events, n (%)	27 (45.8)	20 (51.3)	47 (48.0)
Progression	24 (40.7)	15 (38.5)	39 (39.8)
Death without progression	3 (5.1)	5 (12.8)	8 (8.2)
Number of censored, n (%)	32 (54.2)	19 (48.7)	51 (52.0)
No adequate baseline assessment	0	0	0
Start of new anticancer therapy	11 (18.6)	6 (15.4)	17 (17.3)
Event after missing or inadequate assessments	1 (1.7)	1 (2.6)	2 (2.0)
Withdrawal of consent	1 (1.7)	4 (10.3)	5 (5.1)
Lost to follow-up	1 (1.7)	0	1 (1.0)
No adequate post-baseline tumours assessment	0	1 (2.6)	1 (1.0)
Ongoing without an event	18 (30.5)	7 (17.9)	25 (25.5)
Kaplan-Meier Estimates of Time to Event (Months) Percentiles (95% CI) [a]			
25th	6.0 (4.6, 16.6)	5.4 (1.9, 7.5)	5.6 (3.7, 9.0)
50th	24.9 (15.7, 44.0)	9.3 (6.2, 24.8)	19.5 (9.3, 41.8)
75th	44.0 (41.8, NE)	NE (13.8, NE)	44.0 (41.8, NE)

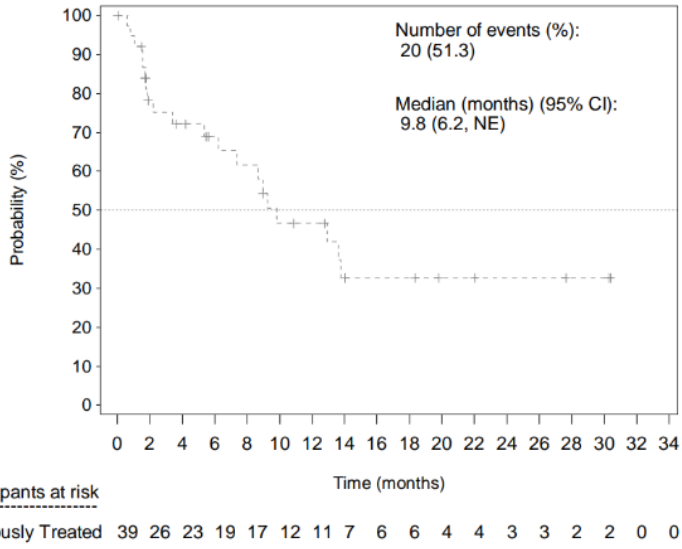
[a] Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

Figure 15: Kaplan-Meier Plot of Progression-Free Survival per RECIST v1.1 According to IRR (Safety Analysis Set) (DCO 22 Sept 2022)

Treatment-naïve participants



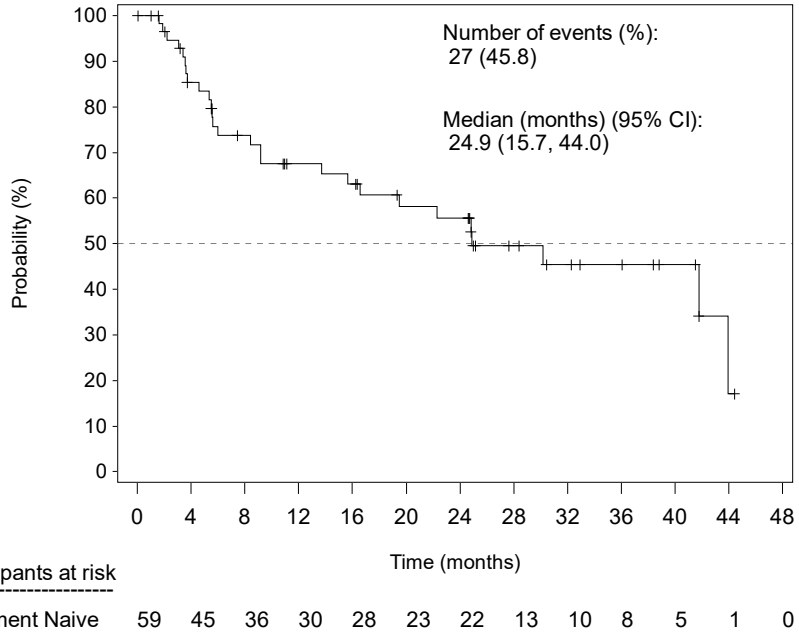
Previously treated participants



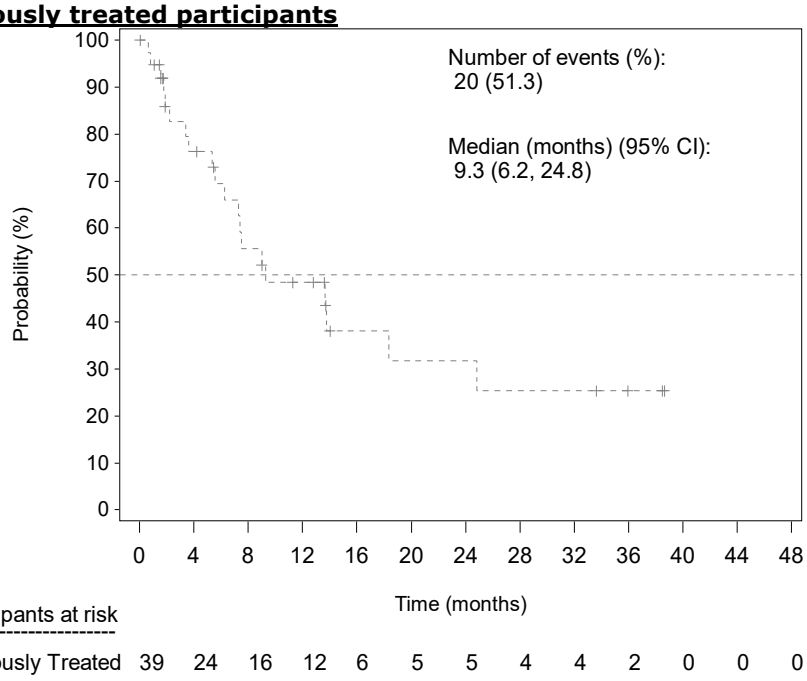
Source PHAROS CSR,
Note: Confidence intervals are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

Figure 16: Kaplan-Meier Plot of Progression-Free Survival per RECIST v1.1 According to IRR (Safety Analysis Set, COD of 19 July 2023)

Treatment-naïve participants



Previously treated participants



Source Table: Table 14.2.12
Note: Confidence intervals are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
\\WILBTIB\WILBTIB08\ARRAY ARR818202\TOPLINE TLF\TLF\fadttec2121.sas
Executed: 24AUG2023 20:53 Data cut date: 19JUL2023

TTR (by IRR and Investigator)

TTR (time to response) is provided as follows:

Treatment-naïve: The median TTR by IRR was 1.86 months (range: 1.1 to 19.1 months).

Previously treated: The median TTR by IRR was 1.74 months (range: 1.2 to 7.3 months).

OS

Treatment-naïve: OS data at the time of PCD, included 17 (28.8%) participants who died and most of participants (40 [67.8%]) still in follow-up for survival.

Previously treated participants: OS data at the time of PCD, included 13 (33.3%) participants who died and a majority of participants (20 [51.3%]) still in follow-up for survival.

The OS at the cut-off date of 19 July 2023 is summarised in **Table 32** and the corresponding Kaplan-Meier curves are provided in **Figure 17**. The median follow-up for OS was 32.1 months in Treatment naïve participants and 28.0 months in Previously treated participants.

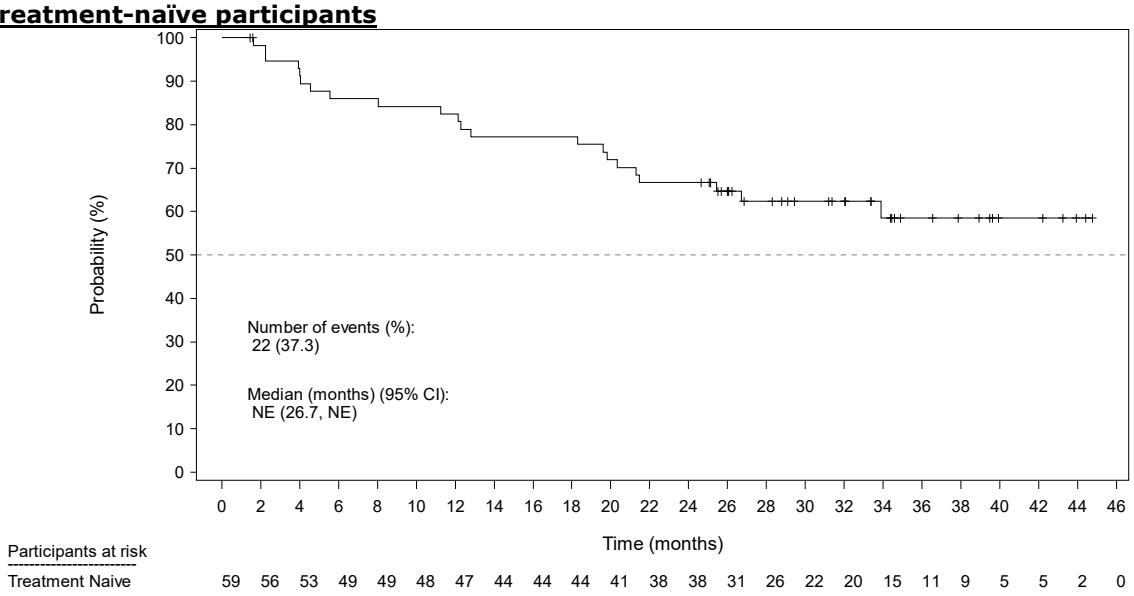
Table 32: Overall Survival (Safety Analysis Set, COD of 19 July 2023)

	Encorafenib+Binimetinib		
	Treatment Naive	Previously Treated	Total
	N=59	N=39	N=98
Number of deaths, n (%)	22 (37.3)	17 (43.6)	39 (39.8)
Number of censored, n (%)	37 (62.7)	22 (56.4)	59 (60.2)
Withdrawal of consent	1 (1.7)	5 (12.8)	6 (6.1)
Lost to follow-up	2 (3.4)	1 (2.6)	3 (3.1)
No longer follow for survival (alive participant who discontinued from the study for reason different from withdrawal consent and lost to follow-up)	0	1 (2.6)	1 (1.0)
Ongoing and no death	34 (57.6)	15 (38.5)	49 (50.0)
Kaplan-Meier Estimates of Time to Event (Months) Percentiles (95% CI) [a]			
25th	19.6 (8.0, 33.9)	8.6 (2.6, 22.7)	12.3 (6.7, 21.5)
50th	NE (26.7, NE)	30.3 (14.1, NE)	NE (26.7, NE)
75th	NE (NE, NE)	NE (32.6, NE)	NE (NE, NE)

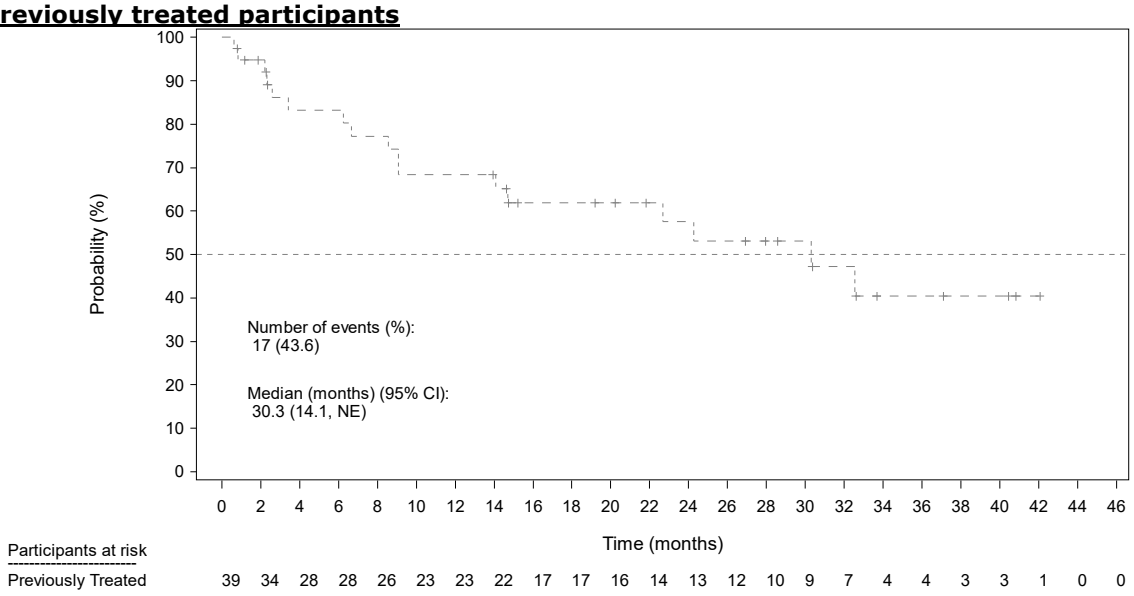
[a] Percentiles with 95% Cis are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

Figure 17: Kaplan-Meier Plot of Overall Survival (Safety Analysis Set, COD of 19 July 2023)

Treatment-naïve participants



Previously treated participants



Note: Confidence intervals are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

Ancillary analyses

Two exploratory endpoints were investigated in PHAROS, namely defined as:

- Plasma concentration-time profiles and PK parameter estimates for encorafenib and its metabolite LHY746 and binimetinib (see sections 2.3.2. to 2.3.5.)
- Genomic analysis of ctDNA in blood samples

Ancillary biomarker analyses (in general, not limited to "liquid biopsy", i.e. blood samples for [genomic] circulating tumour DNA) were conducted as follows:

Participants were eligible for the study based on identification of a BRAF V600 mutation in the tumour or blood as determined by the local laboratory and were required to also submit archival or fresh tissue and blood samples to confirm BRAF V600 mutation status by a central laboratory. Blood samples were also collected and analysed for potential genomic markers and/or proteomic or metabolomic factors and signals.

For tumour tissue, a sample was collected prior to a patient initiating study treatment and was analysed centrally utilizing the FoundationOne CDx assay both for the BRAF V600E mutation status confirmation (IUO, see section "In vitro biomarker test for patient selection for efficacy" below) and for exploratory molecular profiling (RUO). Eighty (80, 82%) screening samples from 48 treatment-naive patients and 32 previously treated patients were available and analysed for genomic alterations. The most frequent genomic alterations identified at baseline, in addition to BRAF status, included SETD2 and TP53 (43% each), SMAD4 (21%), ATM, MLL2, CSF1R, SMARCA4 (14% each), and CDKN2A (11%).

None of these alterations were associated with outcome after false discovery correction (corrected $P < 0.05$) in the overall patient population, treatment-naïve, or previously treated analysis sets.

Although patients commonly had concurrent baseline mutations in several genes, with those with SETD2, TP53, and SMAD4 occurring most frequently, these alterations were not significantly associated with an objective response to treatment.

In addition, ctDNA samples were collected at Screening and at end-of-treatment and tested with the FoundationOne Liquid CDx. BRAF V600E mutation status (IUO, see section "In vitro biomarker test for patient selection for efficacy" below) and other mutations (RUO) potentially interacting with study treatment were assessed using data from a targeted sequencing panel applied to all available Screening samples (98 samples including 59 treatment naive and 39 previously treated patients).

Concerning results of the exploratory endpoint (and objective) ctDNA in blood samples itself, CSR states only that "as sample collection of the exploratory genomic analyses of blood-based ctDNA biomarkers that may be predictive of mutation status has not been completed, results are not available for this CSR."

Subgroup analysis of the primary endpoint

Subgroup analyses of the primary endpoint further are presented below:

Table 33: Objective Response Rate According to IRR by Subgroup (SS) (DCO 22 Sept 2022)

	Encorafenib + Binimetinib								
	Treatment-Naïve			Previously Treated			Total		
Subgroup	n	ORR (%)	95% CI	n	ORR (%)	95% CI	n	ORR (%)	95% CI
Age Group									
<65 years	23	17 (73.9)	(51.6, 89.8)	13	5 (38.5)	(13.9, 68.4)	36	22 (61.1)	(43.5, 76.9)
⩾65 years	36	27 (75.0)	(57.8, 87.9)	26	13 (50.0)	(29.9, 70.1)	62	40 (64.5)	(51.3, 76.3)
Gender									
Female	33	23 (69.7)	(51.3, 84.4)	19	9 (47.4)	(24.4, 71.1)	52	32 (61.5)	(47.0, 74.7)
Male	26	21 (80.8)	(60.6, 93.4)	20	9 (45.0)	(23.1, 68.5)	46	30 (65.2)	(49.8, 78.6)
Race Group									
Asian	3	3 (100)	(29.2, 100)	4	3 (75.0)	(19.4, 99.4)	7	6 (85.7)	(42.1, 99.6)
Non-Asian	56	41 (73.2)	(59.7, 84.2)	35	15 (42.9)	(26.3, 60.6)	91	56 (61.5)	(50.8, 71.6)
ECOG Performance Status									
0	19	14 (73.7)	(48.8, 90.9)	7	6 (85.7)	(42.1, 99.6)	26	20 (76.9)	(56.4, 91.0)
1	40	30 (75.0)	(58.8, 87.3)	32	12 (37.5)	(21.1, 56.3)	72	42 (58.3)	(46.1, 69.8)
Smoking history									
Current/Former	41	29 (70.7)	(54.5, 83.9)	28	13 (46.4)	(27.5, 66.1)	69	42 (60.9)	(48.4, 72.4)
Never	18	15 (83.3)	(58.6, 96.4)	11	5 (45.5)	(16.7, 76.6)	29	20 (69.0)	(49.2, 84.7)
Previous Immunotherapy									
Received at least one IO				24	14 (58.3)	(36.6, 77.9)			
Did not receive any IO				15	4 (26.7)	(7.8, 55.1)			
Previous Anti-Cancer Treatment in metastatic settings									
IO and no chemotherapy				11	7 (63.6)	(30.8, 89.1)			
Chemotherapy and no IO				15	4 (26.7)	(7.8, 55.1)			
IO and chemotherapy				13	7 (53.8)	(25.1, 80.8)			

Data Cut-off 22SEP2022
IO: Immunotherapy
Note: Estimated 95% Cis for ORR was obtained using the exact Clopper-Pearson method.

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 34: Summary of efficacy for PHAROS Study

Title: A Phase 2, Open-label Study of Encorafenib + Binimetinib in Patients with BRAF V600-mutant Non-Small Cell Lung Cancer	
Study identifier	C4221008 (ARRAY-818-202) EudraCT Number 2019-000417-37, NCT03915951 Also known as PHAROS study

Design	PHAROS is a multicentre, open-label, non-comparative, parallel cohorts, Phase 2 study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		14 months after the last participant enrolled in the treatment-naïve cohort (Primary Completion Date). not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Treatment-naïve cohort		59 participants with BRAF V600E-mutant metastatic NSCLC who were treatment-naïve, received study treatment with encorafenib 450 mg QD and binimetinib 45 mg BID administered orally in 28-day (± 3 days) cycles until disease progression.
	Previously treated cohort		39 Participants previously treated in the metastatic setting for their BRAF V600E-mutant metastatic NSCLC received study treatment with encorafenib 450 mg QD and binimetinib 45 mg BID administered orally in 28-day (± 3 days) cycles until disease progression.
Endpoints and definitions	Primary endpoint	ORR per IRR	Objective Response Rate (ORR) as determined by Independent Radiology Review (IRR) per RECIST v1.1
	Secondary endpoint	ORR per Investigator	Objective Response Rate (ORR) derived from Investigator Assessment per RECIST v1.1
	Secondary endpoint	DOR per IRR	Duration of Response (DOR) as determined by Independent Radiology Review (IRR) per RECIST v1.1
	Secondary endpoint	DOR per Investigator	Duration of Response (DOR) derived from Investigator assessment per RECIST v1.1
	Secondary endpoint	PFS per IRR	Progression Free Survival (PFS) as determined by Independent Radiology Review (IRR) per RECIST v1.1

	Secondary endpoint	PFS per Investigator	Progression Free Survival (PFS) derived from Investigator assessment per RECIST v1.1
	Secondary endpoint	OS	Overall Survival
Database lock	19 July 2023		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Safety Set (=Full Analysis Set): All participants who received at least 1 dose of study treatment. Imaging assessments were performed every 8 weeks (± 7 days) after the first dose of study treatment for the first 12 months and then every 12 weeks (± 7 days) until progression, death, initiation of subsequent anticancer therapy or withdrawal of consent.		
Descriptive statistics and estimate variability	Treatment group	Treatment-naïve cohort	Previously treated cohort
	Number of subjects	59	39
	Confirmed ORR per IRR (95% confidence interval [CI])	74.6% (61.6, 85.0)	46.2% (30.1, 62.8)
	Confirmed ORR per Investigator (95% CI)	62.7% (49.1, 75.0)	41.0% (25.6, 57.9)
	DOR per IRR median (95% CI)	40.0 months (23.1 months – NE)	16.7 months (7.4, NE)
	DOR per Investigator median (95% CI)	NE (23.1 months – NE)	12.2 months (10.2 months – NE)
	PFS per IRR median (95% CI)	24.9 months (15.7 months – 44.0)	9.3 months (6.2, 24.8 months)
	PFS per Investigator median (95% CI)	30.5 months (11.1 months – NE)	9.3 months (6.2 months – 13.8 months)

	OS median (95% CI)	NE (26.7 months, NE)	30.3 months (14.1 months, NE)
Effect estimate per comparison	Not applicable	NA	NA
Notes	At the time of Primary Completion Date (22 September 2022), 33 (33.7%) participants were still receiving study treatment, 27 (27.6%) participants had discontinued study treatment but continued to be followed up for disease progression or survival. Thirty-eight (38.8%) participants had discontinued the study. Reasons for discontinuation were: - In the treatment-naïve cohort: death (16 (27.1%) participants), withdrawal of consent (2 (3.4%) participants) and lost to follow up (1 (1.7%) participant) - In the Previously treated cohort: death (13 (33.3%) participants), withdrawal of consent (5 (12.8%) participants) and other reason (1 (2.6%) participant) Most responders in the treatment-naïve population (24 of 44) were still on-treatment with durations of exposure ranging from 15 to 35 months. In the previously treated population, seven of 18 responders were still on-treatment with durations of exposure ranging from 5 to 31 months. Analyses of ORR according to IRR, were generally comparable across sub-populations of baseline and disease characteristics, including age, gender and smoking history, overall and in both study cohorts (treatment-naïve or previously treated participants). As of 19 July 2023, the investigator-assessed ORR slightly increased to 64.4% (95% CI: 50.9, 76.4) including 2 CRs and 36 PRs with one participant switching from SD to PR since the PCD Twenty-three (23.5%) participants were still receiving study treatment, 26 (26.5%) participants had discontinued study treatment but continued to be followed up for disease progression or survival. Forty-nine (350.0%) participants had discontinued the study. Reasons for discontinuation were: - In the treatment-naïve cohort: death (21 (35.6%) participants), withdrawal of consent (2 (3.4%) participants) and lost to follow up (2 (3.4%) participant) - In the Previously treated cohort: death (17 (43.6%) participants), withdrawal of consent (5 (12.8%) participants) and other reason (1 (2.6%) participant) In the treatment-naïve population, 19 of 44 responders were still on-treatment. In the previously treated population, 4 of 18 responders were still on-treatment.		

In vitro biomarker test for patient selection for efficacy

For tumour tissue, a sample was collected prior to a patient initiating study treatment and was analysed centrally utilizing the FoundationOne CDx assay both for the BRAF V600E mutation status confirmation (IUO).

In addition, ctDNA samples were collected at Screening and at end-of-treatment and tested with the FoundationOne Liquid CDx. BRAF V600E mutation status (IUO) were assessed using data from a

targeted sequencing panel applied to all available Screening samples (98 samples including 59 treatment-naive and 39 previously treated patients). End-of-treatment data are under analyses and will be available before end 2024, will be included in the final CSR for the study and should be submitted once available (REC).

Information on the biomarker (BRAF V600E) and the central confirmation test / companion diagnostic(s) (CDx) used in the targeted population in the pivotal study:

Scientific rationale for the choice of the predictive in vitro biomarker test (e.g. prevalence, relation to disease mechanism).

Approximately 1% to 8% of patients with NSCLC have mutations in BRAF, with half of these driven by the BRAFV600E mutation (Class 1) and the other half driven by non-V600E mutations distributed throughout exons 11 and 15 collectively (Class 2 and 3). In 2018, recognizing rapid advances in the field of molecular pathology and new options for targeted therapy, updated recommendations from several professional organizations included a consensus statement that BRAF testing should be performed on all patients with advanced lung adenocarcinoma, irrespective of clinical characteristics.

Encorafenib is a potent and selective ATP competitive inhibitor of BRAFV600-mutant kinase. Mutations in the BRAF gene, such as BRAFV600E, can result in constitutively activated BRAF kinase that may stimulate tumor cell growth. Encorafenib inhibited in vitro growth of tumour cell lines expressing BRAF V600 E, D and K mutations. Binimetinib is a potent and selective allosteric, ATP-uncompetitive inhibitor of MEK1/2. MEK proteins are upstream regulators of the ERK pathway. In vitro, binimetinib inhibited ERK phosphorylation in cell-free assays as well as viability and MEK-dependent phosphorylation of BRAF-mutant human melanoma cell lines. Binimetinib also inhibited in vivo ERK phosphorylation and tumour growth in BRAF-mutant murine xenograft models.

Definition of biomarker / biomarker-positivity including all underlying genetic alterations:

Patients were enrolled into the study based on the presence of a BRAF V600E mutation in tumour tissue or blood (e.g., ctDNA genetic testing, PCR, NGS based assay) as determined by a local laboratory assay (inclusion criterion 4).

The central confirmation of the BRAF V600E mutation status was performed on archival or fresh tumour tissue collected at enrolment and utilized the FoundationOne CDx – F1CDx (tissue) assay as per protocol (inclusion criterion 5).
In addition, blood samples collected at Screening were processed to plasma for the development of another companion diagnostic utilizing the FoundationOne Liquid CDx – F1LCDx (plasma) assay.

The **biomarker-positive definition** is any short variant with protein effect V600E as detected by F1CDx and F1LCDx.

Analytical method including assay platform, specimen, pre-analytical processing requirements and read-out method.

FoundationOne®CDx (F1CDx) is performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumour samples. The assay employs two extraction methods (either DNAx or CoExtraction, an automated DNA/RNA co-extraction methodology) for DNA extraction from routine FFPE biopsy or surgical resection specimens. 50-1000 ng of DNA will then undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons (refer to the F1CDx Technical Label for the complete list of genes included in F1CDx). In total, the assay detects alterations in a total of 324 genes. Using the Illumina® sequencing platform, hybrid capture–

selected libraries are sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data is then processed using a customized analysis pipeline designed to detect all classes of genomic alterations, including base substitutions, indels, copy number alterations (amplifications and homozygous gene deletions), and select genomic rearrangements (e.g., gene fusions). Rearrangements in one of the targeted genes included in the F1CDx technical label may be reported along with their uniquely identified genomic partners, which can be any gene in the genome even if not explicitly targeted by the assay. Additionally, genomic signatures including microsatellite instability (MSI) and tumour mutational burden (TMB) are reported.

FoundationOneLiquid CDx (F1LCDx) is a next generation sequencing based in vitro diagnostic device that analyses 324 genes. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The test also detects tumour fraction and the genomic signatures blood tumour mutational burden (bTMB) and microsatellite instability (MSI). F1LCDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma derived from the anti-coagulated peripheral whole blood of cancer patients. The test is intended to be used as a companion diagnostic to identify patients who may benefit from treatment with targeted therapies in accordance with the approved therapeutic product labelling. Additionally, F1LCDx is intended to provide tumour mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with malignant neoplasms. The assay employs a single DNA extraction method to obtain cfDNA from plasma from whole blood; 20 to 60 ng of DNA will undergo whole-genome shotgun library construction and hybridization-based capture followed by sequencing.

Analytical validation strategy: For verifying the suitability of an assay, robustness, accuracy, specificity, sensitivity and linearity should be considered depending on the analytical platform.

Analytical validation of the F1CDx assay for detecting BRAF V600E was demonstrated by leveraging the platform level validation. These studies included limit of blank, limit of detection, precision, and orthogonal concordance. Specimen type for these studies included extracted DNA from FFPE sections from the FMI clinical archives.

Evidence of the Analytical Performance of F1CDx (central confirmation test)

F1CDx is a CE marked next-generation sequencing (NGS) assay. F1CDx analytical performance has been established through comprehensive validation with a broad range of representative alteration types in various genomic contexts across genes and using specimens from a wide variety of tissue and tumour types. The ability of F1CDx to accurately detect genomic alterations including *BRAF* V600E mutation in NSCLC patient samples have been validated in analytical performance studies, including the limit of detection (LoD) study, the limit of blank (LoB) study, the orthogonal concordance study, and the precision study.

In the platform LoD study, 19 FFPE (Formalin-Fixed Paraffin-Embedded) tumour samples across multiple tumour types (lung cancer, colon cancer, and breast cancer) were assessed including short variants, CNAs (Copy Number Aberrations) and rearrangements.

The platform limit of blank study assessed mutation-negative FFPE sample replicates from clinical samples including non-small cell lung cancer, breast cancer, melanoma, and colorectal cancer. If the percentage of false-positive results did not exceed 5% (type I error risk α=0.05), then the 95% of the result was zero, and the LoB of zero was confirmed. The LoB of zero was confirmed for all variants assessed.

The repeatability and reproducibility of *BRAF* V600E alteration and corresponding 95% two-sided exact CI were also assessed**.**

Table 35: Reproducibility and Repeatability for BRAF short variants

Gene	Number of Unique Samples	CDx Alteration	Alteration of the Sample	Fold LoD[1] as %VAF	Reproducibility (95% exact CI) (%)	Repeatability (95% exact CI) (%)
BRAF	1	V600E	*BRAF* 1799T>A V600E	19.10x	100.0 (90.3, 100.0)	100.0

[1] LoD was determined based on hit rate approach, which is a conservative approach that overestimates LoD. The column represents the level evaluated for the sample in relationship to the LoD for the variant.

The analytical performance of F1CDx in detecting *BRAF* short variants and NSCLC samples have been assessed in multiple studies. The comprehensiveness of the platform validation studies has robustly demonstrated the analytical performance of F1CDx in detecting genomic alterations including alterations in *BRAF* V600E.

Analytical validation of the F1LCDx assay for detecting BRAF V600E was demonstrated through limit of blank, precision and confirmation of limit of detection, and concordance studies. Specimen type for these studies included extracted cfDNA from FMI clinical archives.

Evidence of the Analytical Performance of F1LCDx (developmental assay)

F1LCDx is a CE marked NGS assay and is intended to detect genomic alterations in 324 cancer-related genes across solid tumour types including NSCLC. F1LCDx analytical performance has been established through comprehensive validation with a broad range of representative alteration types in various genomic contexts across genes and using specimens from a wide variety of tissue and tumour types. The ability of F1LCDx to accurately detect genomic alterations including *BRAF* V600E mutation in NSCLC patient samples have been validated in analytical performance studies.

The analytical performance of F1LCDx in detecting *BRAF* short variants and NSCLC samples have been assessed in multiple studies. The comprehensiveness of the platform validation studies has robustly demonstrated the analytical performance of F1LCDx in detecting genomic alterations including alterations in *BRAF* V600E.

Clinical validation strategy / clinical validity (sensitivity/specificity) should be described either by correlation with a clinical endpoint (for novel assays) or - if available - by concordance study with a clinically valid reference assay.

The clinical validity of F1CDx and F1LCDx for detecting BRAF V600E in subjects with NSCLC eligible for treatment with encorafenib in combination with binimetinib was demonstrated in a Phase 2, open-label, multicentre, non-randomized study of specimens from patients enrolled in the PHAROS clinical study. F1CDx and F1LCDx clinical concordance with enrolling local lab tests and clinical bridging analyses using the clinical efficacy data generated from the PHAROS trial demonstrated the clinical validation of the F1CDx and F1LCDx assays for the identification of subjects with BRAF V600E in patients with NSCLC who may benefit from treatment with encorafenib in combination with binimetinib. Clinical validation data will be reviewed by the EMA as part of the submission to the notified body.

Cut-point selection should be described and discussed in detail. Please justify in how far clinical thresholding was performed for cut-point selection of each respective genetic alteration applicable, having in mind this definition has relevant clinical impact for benefit-risk assessment for a "targeted therapy" (efficacy at different cut-points).

The biomarker definition for this CDx consists of BRAF V600E short variants. Detection and reporting of variants by the FMI analysis pipeline are not determined by a singular threshold, but rather by a number of thresholds and quality metrics that are assessed per variant class (*i.e.* short variants, rearrangements, copy number amplifications and losses).

For short variants, de novo assembly was performed by the analysis pipeline using a proprietary algorithm for each target region of interest. The supporting reads for each identified candidate variant were analysed and a number of metrics was calculated and used to evaluate the quality of the variant call. Quality control filtering was applied based on a series of quality control filters which rejected a candidate call based on intrinsic sample noise, the expected noise level for the particular variant and other known error modes such as sequence homology. Variants were reported as biomarker positive if they do not fail the quality control filtering.

To further clarify, one of the factors that determines whether a variant is ultimately called, the limit of detection (LoD), was presented.

For F1CDx, the LoD for each short variant type was assessed and established. The average VAF based on the lowest level with 95% detection rate was established and determined to be 3.2 % VAF.

For F1LCDx, the LoD for each short variant type was assessed and established. The median LoD was also evaluated and determined to be 0.39% VAF.

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

There are currently two other ongoing single arm studies with encorafenib and binimetinib in NSCLC patients, however, none of these studies reached completion at the time of submission of this variation:

- IFCT-1904: A Phase II study of the BRAF inhibitor encorafenib in combination with the MEK inhibitor binimetinib in patients with BRAF V600E-mutant metastatic Non-small Cell Lung Cancer. This is an Investigator-Sponsor trial sponsored by Intergroupe Francophone de Cancerologie Thoracique (IFCT) and is expected to include 119 patients in France (EudraCT 2019-004621-24, NCT04526782). Final CSR is expected by Q2 2026.
- OCEAN II: A Phase II Study Investigating the Combination of encorafenib and binimetinib in BRAF V600E Mutated Chinese Patients With Metastatic Non-Small Cell Lung Cancer. This trial is sponsored by Pierre Fabre and is expected to include 55 homeland Chinese patients (NCT05195632). Final CSR is expected by Q4 2024

Ongoing trial IFCT-1904 has now a design similar to Pharos following an amendment for cohort B (previously treated patients). When this IFCT sponsored trial was started (2021), cohort B was randomized (2:1) to the comparator docetaxel (regulatory second line chemo standard if first line was chemo). 2 patients were treated with docetaxel monotherapy in 2021 (crossover to COMBO 450 offered) until randomization to chemotherapy was omitted by the sponsors.

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Non-Controlled trials	42/98	19/98	1/98

Supportive study(ies)

Not submitted

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

PHAROS is an open label, single arm, multicentre, uncontrolled phase II clinical trial exploring ORR in MEKi/BRAFi naïve patients with stage IV BRAF V600E mutant NSCLC, having 2 (primary endpoint ORR based) null-hypotheses for 2 subgroups, (entirely) naïve patients and pre-treated patients.

This open-label study was amended several times while it was ongoing, including changes in central design elements such as statistical hypotheses, analysis populations and sample size. While only one analysis in the overall population was planned according to the statistical hypothesis in the original study protocol, this was changed to separate analyses for treatment-naïve patients and pre-treated patients in protocol amendment 4. It is also noted that an interim analysis was conducted when the study was almost fully recruited but the follow-up was still ongoing, whereby it is unclear whether persons directly involved in patient treatment or evaluation of progression had knowledge of the results. This is acceptable for an exploratory study, however, in the context of this application where the study is intended to support a new indication, it increases the uncertainties. All enrolled patients received treatment.

The primary endpoint of the PHAROS study was ORR using the RECIST 1.1 assessed by independent radiology review, which is considered acceptable considering the design of the study. Secondary endpoints included DoR, PFS, OS, safety and population pharmacokinetics.

The 6 secondary efficacy (and 1 safety) endpoints listed above are considered as standard approaches in a clinical trial investigating anticancer treatment.

Of note is that (historical) results of two different treatments (dabrafenib plus trametinib, and pembrolizumab respectively) were used for sample size estimation.

By result both null-hypotheses could be rejected separately. This, however, does not mean that it has been confirmed that COMBO 450 is non-inferior, or superior compared to standard first line dabrafenib plus trametinib, or second line pembrolizumab. Rather, and as already stated in the hypotheses of this explorative trial, the results indicate (only) that results as to ORR are "*sufficiently clinically meaningful to warrant further study on encorafenib and binimetinib in this indication where similar therapies are already available".*

Providing exact 95% CIs is a standard approach for ORR in single-arm trials and is acceptable.

It is noted that statistical hypotheses were formulated but these mainly serve to support sample size calculations based on what has been observed for other products in this indication. No statistical tests were performed or p-values provided. This is endorsed, as hypothesis tests for ORR, i.e. excluding ORR smaller than a pre-specified threshold, are considered anyway of limited value as these do not allow to infer clinical benefit (as it is not a validated surrogate for clinically relevant outcomes) or establish superior activity vs other products in this indication (due to the uncertainties of external comparisons). Due to the unclear clinical interpretation, it is also not supported to refer to the statistical hypotheses in the SmPC, where only descriptive results should be provided.

Overall, the statistical methods were appropriate for an exploratory phase 2 study.

The characteristics of the population (age, sex, race, ECOG performance status, smoking status) was generally aligned with what was observed in similar Phase 2 studies of BRAF/MEK inhibitors recently reported in the literature although the Previously treated population had a median age and a proportion of participants with ECOG PS > 0 in the higher spectrum. The low numbers of participants from Black or American African (3.1%) or Asian (7.1%) populations reflects the countries involved in

the pivotal study and is a pattern observed for data sets that informed marketing approvals for several other agents for the treatment of oncogene-addicted NSCLC in the advanced setting.

Efficacy data and additional analyses

The result of the primary endpoint ORR (by IRR confirmed) was **63.3%** in the overall population of PHAROS.

In terms of subgroups (naïve and previously treated), treatment with COMBO450 reveals differences, i.e. an ORR of **74.6 %** (naïve patients, n=59) vs. **46.3%** (previously treated patients, n=39). Potential lower effect in the previously treated patients seems to be driven primarily by the subgroup of (n=15) patients previously treated with 'chemotherapy and no IO'.

Two different subgroup analysis were requested to better understand the effect of prior chemotherapy on ORR. The overall conclusion from these analyses (including those presented for time-to-event endpoints) is that recent (no longer than 12 months ago) chemotherapy may have a negative impact on the outcome of patients treated with COMBO450 (data not shown). The numbers analysed, however, are too small to draw any firm conclusion.

The overall concordance in terms of total agreement rate (82.7%) between ORR per IRR and per investigator assessment is acceptable.

Duration of response remains somehow immature (40.3% of event) and driven by i) higher frequency of responding naïve vs. previously treated patients and ii) higher frequency of censored than observed (progression, survival) events in the overall, and the sub-populations.

Responses, once achieved, seem to be durable in the overall population with a median of 16.7 months for the previously treated subgroup of responders (N=18) and a median of 40.0 months (with lower limit of 95%CI interval of 23.1 months) in the naïve subgroup of responders (N=44).

The same censoring rules were applied as for PFS, i.e. patients were censored at start of new anticancer therapy, which appears to be questionable as the non-informative censoring assumption is unlikely to hold for these patients such that additional analyses were requested (see statistical methods above).

DoR results presented in this report were by IRR assessment. DoR results by investigator, were presented in PHAROS CSR, however, due to the smaller number of responders as assessed by investigator, maturity was lower and less informative (data not shown). Of note, in this analysis median DoR could not be calculated for the naïve patients (55.3% were still responding) whereas median DoR in previously treated patients responding to COMBO450 was 12.2 months.

PFS was included as a secondary endpoint, it is however of limited value in a SAT as it cannot be interpreted in the absence of a comparator.

Ancillary analysis on end of treatment ctDNA data were still ongoing at the time of assessment. According to study protocol, additional ctDNA was planned to be analysed for potential genomic markers of encorafenib and/or binimetinib activity, samples may be for exploratory research investigating genetic variants in ctDNA, such as BRAFV600 mutations as well as additional tumour mutations. Final results from ctDNA Biomarker Analysis should be provided (REC).

Companion diagnostic (CDx) / Biomarker "BRAF V600E-positive"

CDx used for central confirmation

'FoundationOne®CDx (F1CDx)' from tissue biopsy was used as central confirmation test. 98 patient samples were locally tested and eligible (per inclusion criterion 4), the screened and treated patients included 59 treatment naive and 39 previously treated patients. Although inclusion criterion 5 required that a tissue biopsy was confirmed by central testing, five treatment-naïve participants in PHAROS study had V600E mutation not centrally confirmed. Regarding ctDNA samples for liquid biopsy testing by F1LCDx, 80 (82%) screening samples from 48 treatment-naive patients and 32 previously treated patients were available and analysed for genomic alterations.

Definition of biomarker positivity ("BRAF V600E-positive") and its justification

The biomarker-positive definition is any short variant with protein effect V600E as detected by F1CDx and F1LCDx. Although it is noted that the central confirmation testing was only allowed from tissue biopsy, and thus confirmation by F1CDx, the MAH's scientific justification of this definition can be followed.

Analytical method (of central confirmation test)

FoundationOne®CDx (F1CDx) from tissue biopsy was used as central confirmation test for presence of any short variant with protein effect V600E. F1CDx is a CE marked next-generation sequencing (NGS) assay.

Analytical validation strategy (of central confirmation test)

Analytical validation of the confirmatory F1CDx assay for detecting BRAF V600E was demonstrated by leveraging the platform level validation. These studies included limit of blank, limit of detection, precision, and orthogonal concordance. Specimen type for these studies included extracted DNA from FFPE sections from the FMI clinical archives.

Relevant parameters like LoB, LoD, concordance, repeatability, and reproducibility were addressed. The assay is qualitative in nature and determines the LoD by using the hit rate method (defined as the lowest level with ≥ 95% detection) by evaluating variant allele frequency (VAF) for short variants so that the detection and reporting of variants by the FMI analysis pipeline are not determined by a singular threshold. No definite information on, e.g., the tested known short variations/ the genetic aberrations defining a tumour to be biomarker positive was provided.

Analytical validation of the developmental F1LCDx assay for detecting BRAF V600E in liquid biopsies was demonstrated through limit of blank, precision and confirmation of limit of detection, and concordance studies. Specimen type for these studies included extracted cfDNA from FMI clinical archives.

Clinical validation strategy (of central confirmation test)

The MAH stated that the clinical validity of F1CDx and F1LCDx for detecting BRAF V600E in subjects with NSCLC eligible for treatment with encorafenib in combination with binimetinib was demonstrated in a Phase 2, open-label, multicenter, non-randomized study of specimens from patients enrolled in the PHAROS clinical study.

While it is agreed that clinical benefit has been demonstrated for the population selected by local PCR and NGS-based assay results for tumour tissue or blood and confirmed based on the FoundationOne®CDx (F1CDx) assay in tumour tissue, this does not imply clinical validity of the test or its predictive value. A test being clinically valid usually means that it is a predictive test for an effect on clinical outcomes, i.e., the treatment effect in test positive patients is larger than in negative patients (or can even be observed only in test positive patients). Therefore, while an effect on clinical outcomes in the central test positive patients is necessary, this is not sufficient for concluding that the test is predictive, as this would require clinical data in test-negative patients. The justification of clinical validity needs to be based on the clinical rationale in this case.

Cut-point selection (of central confirmation test)

Cut-points for the respective genetic alterations defining "BRAF V600E-positivity" were provided for the central confirmation test 'FoundationOne®CDx (F1CDx)´as 'lower limit of detection' for the qualitative tests for each short variant. The reasoning of cut-off point selection was analytically based, but not clinically, and no clinical thresholding / cut-off testing was performed. Therefore, it remains unclear whether the LoD-based thresholds / cut-off values applied in the targeted BRAF V600E-mutated NSCLC population in the PHAROS study were optimal or whether a lower or higher threshold defining patients as 'BRAF V600E-positive' would lead to a better benefit-risk ratio.

2.4.4. Conclusions on the clinical efficacy

Efficacy claims for encorafenib and binimetinib combination therapy (COMBO450) in a line-agnostic setting in advanced NSCLC with a BRAF V600E genetic alteration are based on the single-arm trial PHAROS. With a confirmed ORR of 74.6% in treatment-naïve stage IV NSCLC patients it can be concluded that COMBO450 treatment is a (highly) active combination in patients harbouring the BRAF V600E mutation. For previously treated patients, the confirmed ORR of 46.2 % is lower but considered relevant. This activity in both subgroups seems to be durable.

2.5. Clinical safety

Introduction

The new indication in NSCLC patients applied for is based on the single arm trial PHAROS investigating, a combination of 45 mg binimetinib twice daily and 450 mg encorafenib once daily (COMBO450). This combination (as well as ENCO300, COMBO300, and 960 mg vemurafenib monotherapy as control) had been extensively investigated in a melanoma population in the 2 parts of RCT CMEK162B2301 (in part 1, 192 melanoma patients were treated with COMBO450), also known as COLUMBUS trial (see initial MA for Mektovi).

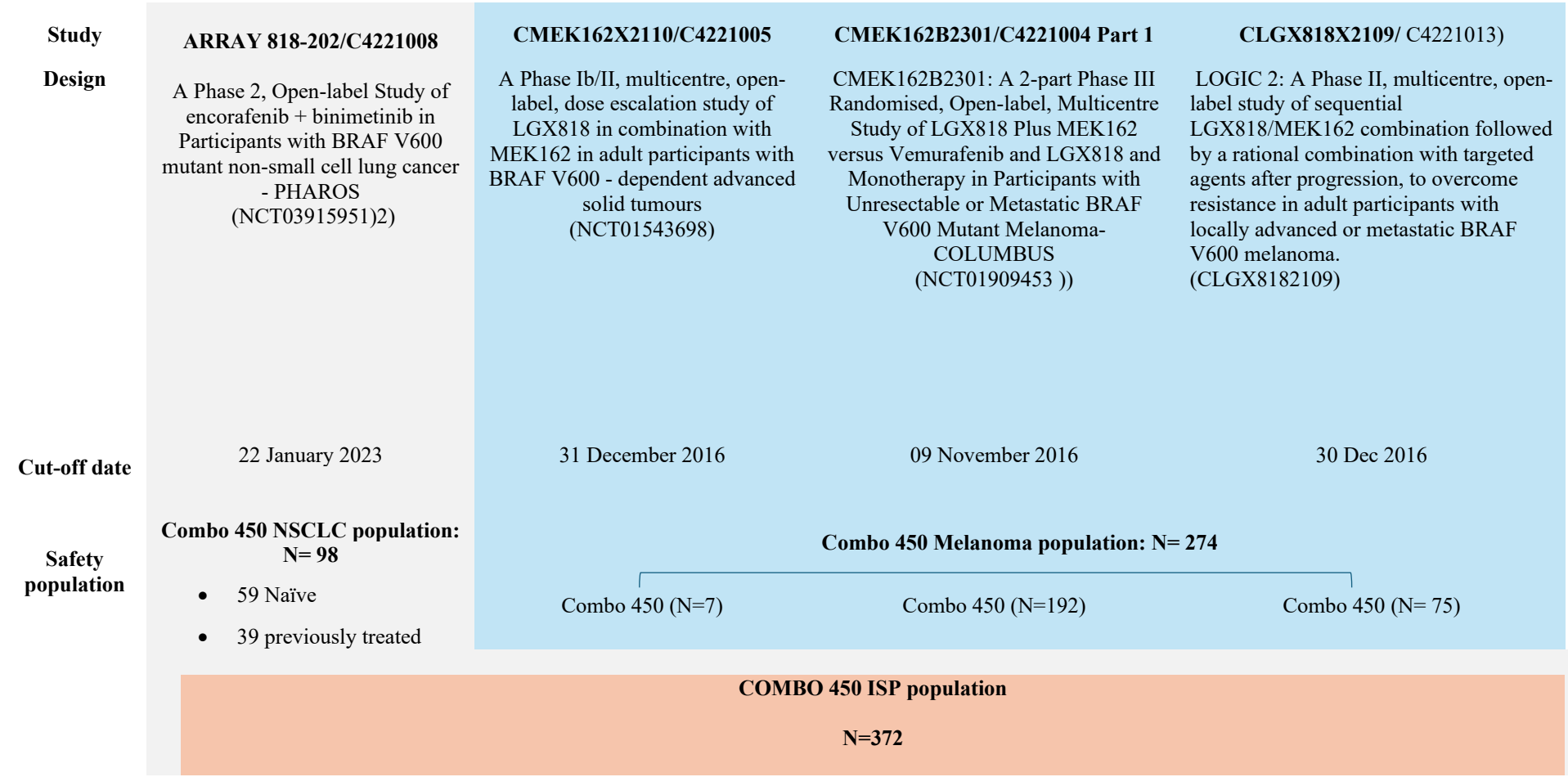
The safety data presented below are based on the PHAROS trial for the NSCLC population, and on a pooled dataset encompassing patients treated at the COMBO450 dose, from 3 melanoma trials (comprising, in addition to COLUMBUS, 2 further SATs in melanoma) and the SAT PHAROS in NSCLC patients.

To ensure that the safety profile of Combo 450 Integrated safey population (ISP) remains aligned with the initially described profile of the combination, and to describe any changes resulting from the introduction of the NSCLC population respectively, to ensure that the safety profile of encorafenib 450 mg QD in combination with binimetinib 45 mg BID observed in the NSCLC population is adequately reflected in Combo 450 ISP, different reviews were conducted:

- Safety profile of Combo 450 ISP against the safety profile of the Melanoma population
- Safety profile of Combo 450 ISP against the safety profile of the NSCLC population
- Safety profile of encorafenib 450 mg QD in combination with binimetinib 45 mg BID in the NSCLC and the Melanoma populations

The source of the actually submitted Combo 450 ISP is displayed in Figure 18 on the next page:

Figure 18: Supportive Clinical Studies with encorafenib 450 mg QD in combination with binimetinib 45 mg BID in the planned NSCLC regulatory application



Combo 450:encorafenib 450 mg QD in combination with binimetinib 45mg

Table 36 below presents a summary of participants disposition for the Safety Set.

In total, 372 participants received at least one dose of Combo 450 and were included in the Safety Set.

In the Combo 450 ISP, 112 participants (30.1%) continued to receive treatment. The most common reasons for discontinuation from study treatment, in all populations, were progressive disease (PD) (65.1%), and adverse event (17.9%).

At the data cut-off for the PHAROS study for the safety analysis for this submission (22 January 2023), 29 participants (29.6%) continued to receive treatment. The most common reason for discontinuation from study treatment, was PD (41.9%).

Table 36: Participants Disposition

	NSCLC Treatment-Naïve (N=59) n (%)	NSCLC Previously Treated (N=39) n (%)	NSCLC Total (N=98) n (%)	Melanoma (N=274) n (%)	Combo 450 ISP (N=372) n (%)
Patients treated					
Treatment ongoing [1]	25 (42.4)	4 (10.3)	29 (29.6)	83 (30.3)	112 (30.1)
Treatment discontinued	34 (57.6)	35 (89.7)	69 (70.4)	191 (69.7)	260 (69.9)
Primary reason for treatment discontinuation					
Adverse Event	12 (35.3)	6 (17.1)	18 (26.1)	24 (12.6)	42 (16.2)
Death	0 (0.0)	3 (8.6)	3 (4.3)	13 (6.8)	16 (6.2)
Investigator Decision	0 (0.0)	1 (2.9)	1 (1.4)	0 (0.0)	1 (0.4)
Lost To Follow-Up	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.4)
Physician Decision	0 (0.0)	0 (0.0)	0 (0.0)	11 (5.8)	11 (4.2)
Progressive Disease	21 (61.8)	20 (57.1)	41 (59.4)	130 (68.1)	171 (65.8)
Protocol Deviation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.4)
Withdrawal by Subject	1 (2.9)	5 (14.3)	6 (8.7)	11 (5.8)	17 (6.5)

NSCLC is corresponding to PHAROS study; Melanoma is corresponding to Melanoma safety pool treated with encorafenib 450 mg QD and binimetinib 45 mg BID; N = number of participants in Safety Set; n = number of participants in analysis; Combo 450 ISP is the pool of NSCLC and Melanoma populations.

Percentages are based on the non-missing data. Counts of missing observations is excluded from the denominator.

[1] Patients ongoing at the time of data extraction.

Sources: W00090_NSCLC - Version date: 30MAY2023 11:27 - File Name: Sub1_1_c1_PatDisp_saf_t.rtf

Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date PHAROS: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023

In the previously treated NSCLC subgroup of trial PHAROS, the vast majority (89.7%) of the patients already discontinued treatment. Main reason was progressive disease – whereas PFS in this subgroup was estimable, and low (9.3 months, IRR).

Patients demographics and baseline characteristics of the NSCLC population are presented in Table 22 and Table 23, characteristics of the melanoma population are presented in the initial marketing authorisation assessment report for Mektovi, INN-binimetinib (europa.eu).

Patient exposure

Combo 450 ISP

In the Combo 450 ISP the median duration of exposure to study treatment (i.e., based on the observed duration and not distinguishing between whether a participant had discontinued treatment or was ongoing at the data cut-off) was 11.04 months. (encorafenib [11.04 months], binimetinib [10.97 months]). Half of participants (50.3%) received ≥ 48 weeks of study treatment.

In the Combo 450 ISP, the median relative dose intensity for encorafenib and binimetinib were 99.6% and 98.9% respectively (Table 37).

NSCLC Population

The NSCLC population had a median duration of exposure to study treatment of 9.5 months (based on the observed duration, not distinguishing between whether a participant had discontinued treatment or was ongoing at the data cut-off) with a lower median duration of exposure in NSCLC Previously treated participants as compared to Treatment-naïve (5.4 months vs 15.1 months respectively at primary completion date and 5.5 and 16.3 at updated DCO)

Table 37: Dose Intensity and Relative Dose Intensity

	NSCLC		Melanoma		Combo 450 ISP	
Dose intensity (mg/day)	ENCO N=98	BINI N=98	ENCO N=274	ENCO N=274	ENCO N=372	BINI N=372
Mean (SD)	388.4 (82.52)	75.9 (17.42)	418.4 (77.01)	81.1 (16.98)	410.5 (79.49)	79.7 (17.22)
Median	446.0	86.1	448.5	89.6	448.0	89.1
Min, Max	169.1; 451.5	2.9; 96.7	150.0; 900.0	6.3; 180.0	150.0; 900.0	2.9; 180.0
Relative dose intensity (%)						
Mean (SD)	86.3 (18.34)	84.4 (19.36)	93.0 (17.11)	90.1 (18.86)	91.2 (17.67)	88.6 (19.14)
Median	99.1	95.6	99.7	99.5	99.6	98.9
Min, Max	37.6; 100.3	3.2; 107.4	33.3; 200.0	6.9; 200.0	33.3; 200.0	3.2; 200.0
Relative dose intensity (%), n (%)						
<50%	5 (5.1)	6 (6.1)	8 (2.9)	15 (5.5)	13 (3.5)	21 (5.6)
50 - <80%	26 (26.5)	28 (28.6)	40 (14.6)	49 (17.9)	66 (17.7)	77 (20.7)
80 - <100%	25 (25.5)	31 (31.6)	96 (35.0)	99 (36.1)	121 (32.5)	130 (34.9)
=100%	40 (40.8)	32 (32.7)	123 (44.9)	109 (39.8)	163 (43.8)	141 (37.9)
>100%	2 (2.0)	1 (1.0)	7 (2.6)	2 (0.7)	9 (2.4)	3 (0.8)

NSCLC is corresponding to PHAROS study; Melanoma is corresponding to Melanoma safety pool treated with encorafenib 450 mg QD and binimetinib 45 mg BID; N = number of participants in Safety Set; n = number of participants in analysis; Combo 450 ISP is the pool of NSCLC and Melanoma populations.

Percentages are based on number of subjects in Safety Set.

Actual dose intensity = Cumulative dose / Duration of exposure.

Relative Dose Intensity (%) = 100 [Actual Dose Intensity / Planned Dose Intensity].

Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date PHAROS: 22JAN2023

Adverse events

Table 38 below provides an overall summary of AEs in the NSCLC and Melanoma populations and the integrated population (Combo 450 ISP). The most common AEs (≥10% in any population) for each of the safety populations are presented by PT in Table 39 (subsequent two pages). The AE profiles of the Combo 450 integrated population and the NSCLC population are presented below and differences between these AE profiles as well as differences with the profile of AEs in the Melanoma population are commented upon, where relevant.

Table 38: Overall Summary of Adverse Events (Safety Set), 22 January 2023 COD

	NSCLC (N=98)		Melanoma (N=274)		Combo 450 ISP (N=372)	
	All grades n (%)	Grade 3+ n (%)	All grades n (%)	Grade 3+ n (%)	All grades n (%)	Grade 3+ n (%)
Adverse events (AEs)	97 (99.0)	69 (70.4)	271 (98.9)	168 (61.3)	368 (98.9)	237 (63.7)
Suspected to be drug-related	92 (93.9)	44 (44.9)	249 (90.9)	95 (34.7)	341 (91.7)	139 (37.4)
Serious Adverse events (SAEs)	43 (43.9)	37 (37.8)	110 (40.1)	94 (34.3)	153 (41.1)	131 (35.2)
Suspected to be drug-related	14 (14.3)	11 (11.2)	31 (11.3)	22 (8.0)	45 (12.1)	33 (8.9)
AEs leading to treatment discontinuation	17 (17.3)	7 (7.1)	32 (11.7)	26 (9.5)	49 (13.2)	33 (8.9)
Suspected to be drug-related	17 (17.3)	7 (7.1)	16 (5.8)	10 (3.6)	33 (8.9)	17 (4.6)
AEs requiring treatment dose interruption and/or dose adjustment	68 (69.4)	45 (45.9)	143 (52.2)	94 (34.3)	211 (56.7)	139 (37.4)
Suspected to be drug-related	56 (57.1)	32 (32.7)	116 (42.3)	67 (24.5)	172 (46.2)	99 (26.6)
AEs requiring additional therapy [1]	92 (93.9)	45 (45.9)	246 (89.8)	110 (40.1)	338 (90.9)	155 (41.7)
Suspected to be drug-related	73 (74.5)	20 (20.4)	175 (63.9)	40 (14.6)	248 (66.7)	60 (16.1)

NSCLC is corresponding to PHAROS study; Melanoma is corresponding to Melanoma safety pool treated with encorafenib 450 mg QD and binimetinib 45 mg BID; N = number of participants in Safety Set; n = number of participants in analysis; Combo 450 ISP is the pool of NSCLC and Melanoma populations.

Percentages are based on number of subjects in Safety Set.

A patient is counted once within each category.

Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date PHAROS: 22JAN2023 - Dataset ADSP1.ADAE:24JUL2023 ADSP1.ADSL:27JUN2023

Table 39: Adverse Events, Regardless of Study Drug Relationship, by Preferred Term and Treatment – Overall and Grade ≥3 (≥10% in population) (Safety Set, DCO 22 January 2023)

	NSCLC (N=98)		Melanoma (N=274)		Combo 450 ISP (N=372)	
Preferred Term	**All grades n (%)**	**Grade 3+ n (%)**	**All grades n (%)**	**Grade 3+ n (%)**	**All grades n (%)**	**Grade 3+ n (%)**
Any preferred term	97 (99.0)	69 (70.4)	271 (98.9)	168 (61.3)	368 (98.9)	237 (63.7)
Nausea	57 (58.2)	4 (4.1)	114 (41.6)	7 (2.6)	171 (46.0)	11 (3.0)
Diarrhoea	51 (52.0)	5 (5.1)	104 (38.0)	9 (3.3)	155 (41.7)	14 (3.8)
Fatigue	44 (44.9)	4 (4.1)	85 (31.0)	6 (2.2)	129 (34.7)	10 (2.7)
Vomiting	39 (39.8)	1 (1.0)	77 (28.1)	6 (2.2)	116 (31.2)	7 (1.9)
Arthralgia	15 (15.3)	1 (1.0)	80 (29.2)	2 (0.7)	95 (25.5)	3 (0.8)
Constipation	26 (26.5)	0	66 (24.1)	0	92 (24.7)	0
Blood creatine phosphokinase increased	15 (15.3)	3 (3.1)	74 (27.0)	16 (5.8)	89 (23.9)	19 (5.1)
Anaemia	32 (32.7)	13 (13.3)	51 (18.6)	13 (4.7)	83 (22.3)	26 (7.0)
Pyrexia	22 (22.4)	0	47 (17.2)	7 (2.6)	69 (18.5)	7 (1.9)
Headache	10 (10.2)	0	57 (20.8)	4 (1.5)	67 (18.0)	4 (1.1)
Abdominal pain	19 (19.4)	0	47 (17.2)	5 (1.8)	66 (17.7)	5 (1.3)
Vision blurred	20 (20.4)	1 (1.0)	43 (15.7)	1 (0.4)	63 (16.9)	2 (0.5)
Asthenia	16 (16.3)	4 (4.1)	43 (15.7)	3 (1.1)	59 (15.9)	7 (1.9)
Oedema peripheral	21 (21.4)	0	35 (12.8)	3 (1.1)	56 (15.1)	3 (0.8)
Dizziness	18 (18.4)	1 (1.0)	34 (12.4)	4 (1.5)	52 (14.0)	5 (1.3)
Alopecia	12 (12.2)	0	38 (13.9)	0	50 (13.4)	0
Back pain	20 (20.4)	1 (1.0)	30 (10.9)	2 (0.7)	50 (13.4)	3 (0.8)
Dry skin	14 (14.3)	0	36 (13.1)	0	50 (13.4)	0
Myalgia	12 (12.2)	2 (2.0)	38 (13.9)	1 (0.4)	50 (13.4)	3 (0.8)

	NSCLC (N=98)		Melanoma (N=274)		Combo 450 ISP (N=372)	
Preferred Term	**All grades n (%)**	**Grade 3+ n (%)**	**All grades n (%)**	**Grade 3+ n (%)**	**All grades n (%)**	**Grade 3+ n (%)**
Rash	12 (12.2)	1 (1.0)	38 (13.9)	2 (0.7)	50 (13.4)	3 (0.8)
Alanine aminotransferase increased	13 (13.3)	5 (5.1)	36 (13.1)	13 (4.7)	49 (13.2)	18 (4.8)
Muscle spasms	12 (12.2)	0	37 (13.5)	1 (0.4)	49 (13.2)	1 (0.3)
Dyspnoea	26 (26.5)	8 (8.2)	21 (7.7)	1 (0.4)	47 (12.6)	9 (2.4)
Pruritus	15 (15.3)	0	32 (11.7)	1 (0.4)	47 (12.6)	1 (0.3)
Cough	16 (16.3)	0	27 (9.9)	1 (0.4)	43 (11.6)	1 (0.3)
Gamma-glutamyltransferase increased	2 (2.0)	2 (2.0)	40 (14.6)	23 (8.4)	42 (11.3)	25 (6.7)
Aspartate aminotransferase increased	15 (15.3)	7 (7.1)	26 (9.5)	6 (2.2)	41 (11.0)	13 (3.5)
Hyperkeratosis	5 (5.1)	0	36 (13.1)	1 (0.4)	41 (11.0)	1 (0.3)
Pain in extremity	12 (12.2)	2 (2.0)	29 (10.6)	4 (1.5)	41 (11.0)	6 (1.6)
Hypertension	9 (9.2)	4 (4.1)	31 (11.3)	15 (5.5)	40 (10.8)	19 (5.1)
Blood creatinine increased	16 (16.3)	0	19 (6.9)	3 (1.1)	35 (9.4)	3 (0.8)
Decreased appetite	14 (14.3)	1 (1.0)	21 (7.7)	0	35 (9.4)	1 (0.3)
Insomnia	11 (11.2)	0	23 (8.4)	0	34 (9.1)	0
Blood alkaline phosphatase increased	11 (11.2)	2 (2.0)	20 (7.3)	2 (0.7)	31 (8.3)	4 (1.1)
Nasopharyngitis	1 (1.0)	0	30 (10.9)	0	31 (8.3)	0
Lipase increased	15 (15.3)	9 (9.2)	14 (5.1)	7 (2.6)	29 (7.8)	16 (4.3)
Ejection fraction decreased	10 (10.2)	1 (1.0)	18 (6.6)	2 (0.7)	28 (7.5)	3 (0.8)
Weight increased	11 (11.2)	1 (1.0)	15 (5.5)	2 (0.7)	26 (7.0)	3 (0.8)
Hyponatraemia	12 (12.2)	10 (10.2)	3 (1.1)	1 (0.4)	15 (4.0)	11 (3.0)
Productive cough	11 (11.2)	0	3 (1.1)	0	14 (3.8)	0
COVID-19	10 (10.2)	0	0	0	10 (2.7)	0

AE = Adverse Event; NSCLC is corresponding to PHAROS study; Melanoma is corresponding to Melanoma safety pool treated with encorafenib 450 mg QD and binimetinib 45 mg BID; N = number of participants in Safety Set; n = number of participants in analysis; Combo 450 ISP is the pool of NSCLC and Melanoma populations.

Percentages are based on number of subjects in Safety Set.

Preferred terms (PT) are sorted in descending frequency, as reported in the 'Combo 450 ISP' all Grade column.

A participant with more than one occurrence of the same adverse event in a particular PT is counted only once in the total of those experiencing adverse events in that particular PT.

MedDRA Version 25.1 has been used for the reporting of adverse events.

- Version date: 27JUN2023 17:33

AE profile of Combo 450 ISP

AEs resulted in **on-treatment death** in 8 (2.2%) of participants). These AEs were myocardial infarction (NSCLC population), haemorrhage intracranial (NSCLC population), cerebral haemorrhage (Melanoma population), multiple organ dysfunction syndrome (Melanoma population), death (2 events, Melanoma population), euthanasia (Melanoma population) and committed suicide (Melanoma population).

The most common **SAEs** (≥ 2% of participants) were pneumonia and anaemia (2.2% each).

The most frequently reported **AEs leading to discontinuation** of all study treatment (≥ 1% of participants) by PT were ALT increased and AST increased (1.3% each), and blood creatinine increased (1.1%).

The most frequent **AEs leading to dose modification** of all study treatments (≥ 5 % in incidence) by PT were nausea (9.7%), diarrhoea (8.1%), vomiting (7.0%), ALT increased (5.6%) and ejection fraction decreased (5.1%).

The most frequent **AEs requiring additional therapy** (≥ 10% in incidence) by PT were nausea (26.6%), diarrhoea (16.9%), constipation (14.2%) and anaemia (11.3%).

AE profile of NSCLC Population

There were 2 (2.0%) deaths within 30 days of last study treatment administration that were due to adverse events (myocardial infarction considered not related by the investigator and haemorrhage intracranial considered related to study treatment by the investigator).

The most frequently reported SAEs (≥ 2% of participants) by PT were disease progression (6.1%), neoplasm progression and colitis (4.1% each), anaemia and dyspnoea (3.1% each), pneumonia, pleural effusion, oedema peripheral, myocardial infarction, haemothorax, device related infection and atrial fibrillation (2% each).

The most frequently reported AEs leading to discontinuation of all study treatments (≥ 2% of participants) were diarrhoea, nausea, vomiting, myalgia and ejection fraction decreased (2.0% each).

The most frequent AEs leading to dose modification of all study treatments (≥ 5 % in incidence) by PT were by PT were diarrhoea (18.4%), nausea (16.3%), vomiting (9.2%), fatigue, anaemia and AST increased (7.1% each) and ALT increased (6.1%).

The percentage of participants with AEs requiring additional therapy was 93.9% (45.9% due to Grade ≥3 events). The most frequent AEs requiring additional therapy (≥ 10% in incidence) by PT were nausea (42.9%), diarrhoea (24.5%), constipation (17.3%), anaemia (16.3%), vomiting (15.3%), back pain (14.3%) and pruritus (10.2%).

AE profile of NSCLC Population vs AE profile of Melanoma population

Differences between the NSCLC and Melanoma populations AE profiles are detailed below. Absolute differences in incidence of ≥10% between NSCLC and Melanoma populations (all grades AEs) or/and of ≥2% for Grade ≥ 3 AEs are described in **Table 40**.

The key differences were:

- AEs of nausea (58.2% vs 41.6%), anaemia (32.7% vs 18.6%), lipase increased (15.3% vs 5.1%), hyponatraemia (12.2% vs 1.1%), productive cough (11.2% vs 1.1%), and as expected, COVID19 (10.2% vs none),

  AEs of arthralgia (15.3% vs 29.2%), headache (10.2% vs 20.8%), blood CK increased (15.3% vs 27.0%), and GGT increased (2.0% vs 14.6%) were reported at a higher incidence

(≥ 10% absolute difference) in the Melanoma than the NSCLC population. Assessments of lipase, GGT and CPK were different in the NSCLC and Melanoma studies, which explains the differences observed between the NSCLC and Melanoma populations.

- Less common AEs (overall incidence <10% in the Melanoma population) of cough (16.3% vs 9.9%), blood creatinine increased (16.3% vs 6.9%), aspartate aminotransferase increased (15.3% vs 9.5%), decreased appetite (14.3% vs 7.7%), weight increased (11.2% vs 5.5%), non-cardiac chest pain (8.2% vs 2.9%), SARS-CoV-2 test positive (8.2% vs none), hypalbuminaemia (7.1% vs 0.7%), colitis (6.1% vs 1.1%) and disease progression (6.1% vs none).
- AEs of upper respiratory tract infection (4.1% vs 9.1%), skin papilloma (2% vs 7.3%), erythema (2% vs 7.3%). nasopharyngitis (1.0% vs 10.9%), retinopathy (none vs 9.1%), subretinal fluid (none vs 7.7%), and palmoplantar keratoderma (none vs 7.7% %) visual field defects (none vs 6.2%) and macular oedema, (none vs 5.1%) were reported at a higher incidence (≥ 5% absolute difference) in the Melanoma than the NSCLC population.

Across NSCLC and Melanoma populations, Grade ≥3 AEs of anaemia (13.3% vs 4.7%), hyponatraemia (10.2% vs 0.4%), lipase increased (9.2% vs 2.6%) and dyspnoea (8.2% vs 0.4%) were reported at a higher incidence (≥5% difference in absolute incidence) in the NSCLC than the Melanoma population. The Grade ≥3 AE of GGT increased (2.0% vs 8.4%) was the only AE reported at a higher incidence (≥ 5% difference in absolute incidence) in the Melanoma than the NSCLC population.

Incidence rates of on-treatment deaths were similar across melanoma and NSCLC population with most deaths due to progression of malignant disease.

There was no remarkable difference (≥2% difference in incidence) in the profile of SAEs in the NSCLC and Melanoma populations.

Across NSCLC and Melanoma populations, incidence rates of AEs leading to study drug discontinuation of all study treatments were similar, overall (17.3% vs 11.7%), and for Grade ≥3 AEs (7.1% vs 9.5%). There was no remarkable difference (<2% absolute difference) in the profile of AEs leading to study drug discontinuation in the NSCLC and Melanoma populations.

Overall and Grade ≥3 incidences of AEs requiring dose modification of study treatment were higher in the NSCLC than in the Melanoma population (overall: 69.4% vs 52.2% and Grade ≥3 AEs: 45.9 vs 34.3%). Incidences of individual AEs that required dose modification were similar between the two populations, with the following exceptions:

- Higher incidence overall (≥ 5% absolute difference) in the NSCLC than the Melanoma population: diarrhoea (18.4% vs 4.4%), nausea (16.3% vs 7.3%), and anaemia (7.1 vs 1.8%).
- No individual AEs leading to dose modification was reported at a lower incidence in the NSCLC population than in the Melanoma population (absolute difference ≥ 5%).

Across the NSCLC and Melanoma populations, notable differences in AEs newly occurring or worsening during the first month of treatment include:

- Grade ≥3 AEs occurred more frequently in the NSCLC population than in the Melanoma population (28.6% vs 17.5%).
- AEs (all grades) of nausea, diarrhoea, fatigue and vomiting occurred more frequently in the NSCLC population than in the Melanoma population (≥10% absolute difference in all Grade AE frequencies).

When analysing the temporality of events, i.e. the proportion of first-occurrence or worsening overtime, the following AEs occurred earlier (higher proportion of first onset during the first two Months) in the NSCLC than in the Melanoma population: nausea, vomiting, pyrexia, abdominal pain, fatigue and asthernia. ALT increased, hypertension and lipase increased occureed earlier in the Melanoma than the NSCLC population.

Table 40: Tolerability Profile for AEs with a relevant difference in Incidence (≥10% Overall or/and ≥2% Grade≥3) between NSCLC and Melanoma Population (Safety set)

	AE/PT	AES (NSCLC vs Melanoma)		AEs leading to discontinuation (NSCLC vs Melanoma)	AEs leading to dose modification (NSCLC vs Melanoma)		AEs Requiring Additional therapy (NSCLC vs Melanoma)			
		Overall	**Grade ≥3**	**Serious AEs**	**Overall**	**Grade ≥3**	**Overall**	**Grade ≥3**	**Overall**	**Grade ≥3**
	Any PT	99.0% vs 98.9%	69% vs 61.3%	43.9% vs 40.1%	17.3% vs 11.7%	7.1% vs 9.5%	69.4% vs 52.2%	45.9% vs 34.3%	93.9% vs 89.8%	45.9% vs 40.1%
Higher in NSCLC	Nausea	58.2% vs 41.6%	4.1 % vs 2.6%	1.0% vs 2.2%	2.0% vs 0.4%	None	16.3% vs 7.3%	3.1% vs 1.5%	42.9% vs 20.8%	3.1% vs 2.2%
	Diarrhoea	52.0% vs 38.0%	5.1% vs 3.3%	1.0% vs 1.5%	2.0% vs 0.4%	None	18.4% vs 4.4%	4.1 vs 1.1%	24.5% vs 14.2%	3.1% vs 2.2%
	Fatigue	44.9% vs 31.0%	4.1% vs 2.2%	None vs 0.7%	1.0% vs 0.4%	None	9.2% vs 6.2%	None vs 0.7%	None vs 0.7%	none
	Vomiting	39.8% vs 28.1%	1.0% vs 2.2%	None vs 1.8%	None	None	9.2% vs 6.2%	None vs 0.7%	15.3% vs 7.7%	None vs 0.3%
	Anaemia	32.7% vs 18.6%	13.3% vs4.7%	3.1% vs 1.8%	1.0% vs 0.4%	1.0% vs 0.4%	7.1% vs 1.8%	5.1% vs0.7%	16.3% vs 9.5%	12.2% vs 3.6%
	Dyspnoea	26.5% vs7.7%	8.2% vs 0.4%	3.1% vs 0.4%	None		3.1% vs 0.4%	3.1% vs none	9.2% vs 1.1%	5.1% vs 0.4%
	Lipase increased	15.3% vs5.1%	9.2% vs2.6%	None	1.0% vs none	1.0% vs none	4.1% vs 2.6%	3.1% vs 2.6%	None	None

	Hyponatraemia	12.2% vs1.1%	10.2% vs0.4%	1.0% vs none	None	None	3.1% vs none	3.1% vs none	5.1% vs none	5.1% vs none
	Productive cough	11.2% vs1.1%	None	None	None	None	None	None	4.1% vs 0.4%	None
	Covid 19	10.2% vs none	None	2.0 vs none	None	None	3.1% vs none	None	6.1% vs none	1.0 vs none
	Asthenia	16.3% vs 15.7%	4.1% vs 1.1%	1.0% vs 0.4%	1.0% vs 0.4%	1.0% vs 0.4%	4.1% vs 1.1%	4.1% vs none	1.0% vs none	None
	AST increased	15.3% vs 9.5%	7.1% vs 2.2%	None	None vs 1.8%	None vs 0.7%	7.1% vs 3.6%	5.1% vs 0.7	None vs 0.7%	None v 0.4%
	Colitis	6.1% vs 1.1%	3.1% vs 0.7%	4.1% vs 0.7%	1.0% vs none	1.0% vs none	3.1% vs 0.7%	2.0% vs 0.7%	5.1% vs 0.7%	3.1% vs 0.7%
	Respiratory failure	2.0% vs none	2.0% vs none	None	None	None	None	None	None	None
Higher in Melanoma	Arthralgia	15.3% vs29.2%	1.0% vs 0.7%	None	1.0% vs none	None	2.0% vs 2.6%	1.0% vs 0.4%	4.1% vs 9.9%	None vs 0.4%
	Blood CK increased	15.3% vs27.0%	3.1% vs 5.8%	None vs 0.4%	1.0% vs 0.4%	None	3.1% vs 2.9%	2.0% vs 1.5%	None vs 0.4%	None
	Headache	10.2%vs20.8%	None vs 1.5%	None vs 0.7%	None	None	None vs 1.1%	None vs 0.7%	4.1% vs 7.7%	None vs 1.5%
	GGT increased	2.0% vs14.6%	2.0 vs 8.4%	None	None	None	None vs 3.6%	None vs 2.9%	None vs 0.4%	None vs 0.4%
	Pyrexia	22.4% vs 17.2%	None vs 2.6%	None vs 2.2%	None	None	1.0% vs 3.6%	None vs 1.5%	9.2% vs 8.8%	None vs 2.2%

Neoplasm progression and disease progression excluded

Adverse events of special interest(AESI)

Adverse Events of Special Interest were analysed in the NSCLC population to determine if any AESIs not yet reported as ADRs should be evaluated as potential ADRs.

The list of AESIs was kept unchanged as compared to the one evaluated in the addendum to Melanoma Module 2.7.4 of the initial MAA of encorafenib and binimetinib. All AESI groupings were defined prospectively through the use of SMQs, HLTs, SOCs or grouping of PTs or through a combination of these components. Occasionally the SMQs, HLTs, SOCs or groupings of PTs used for the definition of ADRs (that were defined retrospectively) may differ from what was used for the corresponding AESIs (as the ADR may be more specific that the AESI), explaining differences in frequencies between AESIs and ADRs for AESIs that have translated into ADRs.

The AESIs include groupings that have become ADRs of encorafenib and / or binimetinib and other groupings that are not ADRs of encorafenib and/or binimetinib in the approved melanoma indication. The AESI groupings that are not ADRs are: Tachycardia, Skin infections, Nail disorders, Hepatic failure, Severe cutaneous adverse reactions, Cutaneous non-squamous cell carcinoma, Melanoma, Bradycardia, Pneumonitis, and Retinal vein occlusion.

Table 41 presents an overview of AESIs of encorafenib and binimetinib regardless of causality, by grouping and preferred term - overall and for Grade ≥3 as of 22 January 2023 cut-off date.

Table 41: Adverse Events of Special Interest, Regardless of Relationship to Study Drug, by Grouping – Overall and Maximum Grades 3 and 4 (Safety Set)

Grouping	NSCLC Total (N=98)	Melanoma Total (N=274)
AESIs Common to Both Binimetinib and Encorafenib		
Rash	25 (25.5)	65 (23.7)
Grade 3+	2 (2.0)	2 (0.7)
Liver function test abnormalities	19 (19.4)	69 (25.2)
Grade 3+	10 (10.2)	34 (12.4)
Myopathy	18 (18.4)	44 (16.1)
Grade 3+	3 (3.1)	2 (0.7)
Haemorrhage	15 (15.3)	43 (15.7)
Grade 3+	5 (5.1)	7 (2.6)
Tachycardia	10 (10.2)	5 (1.8)
Grade 3+	3 (3.1)	1 (0.4)
Skin infections	8 (8.2)	31 (11.3)
Grade 3+	3 (3.1)	4 (1.5)
Acute renal failure	4 (4.1)	8 (2.9)
Grade 3+	1 (1.0)	5 (1.8)
Nail disorders	3 (3.1)	5 (1.8)
Grade 3+	0	0
Photosensitivity	3 (3.1)	10 (3.6)
Grade 3+	0	1 (0.4)
Hepatic failure	0	1 (0.4)
Grade 3+	0	0
Severe cutaneous adverse reactions	0	2 (0.7)
Grade 3+	0	0
AESIs Specific to Encorafenib		
Cutaneous squamous cell carcinoma	3 (3.1)	7 (2.6)
Grade 3+	1 (1.0)	0
Palmar-plantar erythrodysaesthesia syndrome	2 (2.0)	17 (6.2%)
Grade 3+	0	0

Grouping	NSCLC Total (N=98)	Melanoma Total (N=274)
Facial paresis	1 (1.0)	2 (0.7)
Grade 3+	0	1 (0.4)
Uveitis type events	1 (1.0)	8 (2.9)
Grade 3+	0	1 (0.4)
Cutaneous non-squamous cell carcinoma	0	5 (1.8)
Grade 3+	0	0
Melanomas	0	0
Grade 3+	0	0
AESIs Specific to Binimetinib		
Retinopathy excluding RVO	30 (30.6)	144 (52.6)
Grade 3+	2 (2.0)	6 (2.2)
Peripheral oedema	24 (24.5)	40 (14.6)
Grade 3+	1 (1.0)	2 (0.7)
Muscle enzyme/protein changes	15 (15.3)	74 (27.0%)
Grade 3+	3 (3.1)	16 (5.8%)
Left ventricular dysfunction	13 (13.3)	23 (8.4)
Grade 3+	2 (2.0)	3 (1.1)
Hypertension	9 (9.2)	33 (12.0)
Grade 3+	4 (4.1)	17 (6.2)
Venous thromboembolism	3 (3.1)	11 (4.0)
Grade 3+	0	2 (0.7)
Pneumonitis	2 (2.0)	1 (0.4)
Grade 3+	0	0
Bradycardia	1 (1.0)	4 (1.5)
Grade 3+	0	0
Retinal vein occlusion	0	0
Grade 3+	0	0
Rhabdomyolysis	0	1 (0.4)
Grade 3+	0	1 (0.4)

AESI = Adverse Event of Special Interest; N = number of participants in Safety Set; n = number of participants in analysis. Percentages are based on number of subjects in Safety Set.
MedDRA Version 25.1 has been used for the reporting of adverse events
Sources: W00090_NSCLC - Version date: 30MAY2023 16:17 - File Name: Sub2_6_1_c1_AESI_saf_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date PHAROS: 22JAN2023 - Dataset AD1X1.ADAESI:19APR2023 AD1X1.ADSL:19APR2023 - PGM Sub2_6_1_c1_AESI_saf_t.sas 30MAY2023 16:16

Overall, the pattern of AESIs in the NSCLC population is coherent with that observed in the first marketing application of encorafenib and binimetinib in the Melanoma population.

Integrated list of Adverse drug reactions (ADRs)

The list of ADRs for the Combo 450 ISP includes the ADRs defined in the initial MAA and reflected in the Mektovi current SmPC. No new ADRs have been identified following the review of individual AEs in the NSCLC and Combo ISP populations and the review of AESIs not previously reported as ADRs in the NSCLC population.

Of note, PTs of AEs contributing to ADR groupings that occurred in the Melanoma population were recoded using MedDRA version 25.1 (previously version 19.0) to align with the MedDRA version used for the coding of AEs in the NSCLC population.

The most noticeable change in frequency resulting from the up-versioning of MedDRA coding of the Melanoma population adverse events is for the ADR grouping "Arthralgia". Using MedDRA V19.0, there were 10 AEs initially coded to the preferred term "musculoskeletal pain" (a PT that is not part of the Arthralgia ADR grouping), however using MedDRA V25.1 the preferred term for these 10 AEs is

"arthralgia" (which is a PT part of the Arthralgia ADR grouping), leading to a 2.2% increase of the Arthralgia ADR frequency. However, this increase has no impact on the frequency category (very common), which remains unchanged.

All other changes led to variations in frequency <1% and did not trigger any change in frequency category.

ADRs occurred in 98.1% of participants in the Combo 450 ISP with 48.79% Grade ≥3 events. The most common ADRs (≥25%) were fatigue (48.1%), nausea (46.0%), diarrhoea (41.7%), vomiting (31.2%), abdominal pain (28.5%), myopathy/muscular disorder (26.1%) and arthralgia (25.8%) (Table 42). Median time to first ADR (Kaplan-Meier in participants with events) was 0.13 [0.03-12.98] months.

Table 42: Uncommon, Common and Very Common ADRs of Combo 450 ISP (Safety Set; N=372)

System Organ Class	Adverse drug reactions	Frequency (All grades)	Frequency Category (All grades)	Grade 3+
Blood and Lymphatic System Disorders	Anaemia	23.1%	Very common	7.0%
Cardiac Disorders	Left ventricular dysfunction (Cardiomyopathy)	9.4%	Common	1.3%
Eye Disorders	Visual impairment	23.1%	Very common	0.8%
	Retinal pigment epithelial detachment	22.3%	Very common	1.6%
	Uveitis	3.5%	Common	0.3%
Gastrointestinal Disorders	Nausea	46.0%	Very common	3.0%
	Diarrhoea	41.7%	Very common	3.8%
	Vomiting	31.2%	Very common	1.9%
	Abdominal pain	28.5%	Very common	2.2%
	Constipation	24.7%	Very common	0.0%
	Colitis	3.2%	Common	1.3%
	Pancreatitis	0.8%	Uncommon	0.8%
General Disorders and Administration Site Conditions	Fatigue	48.1%	Very common	4.3%
	Pyrexia	18.5%	Very common	2.2%
	Peripheral oedema	17.2%	Very common	1.1%
Immune System Disorders	Drug hypersensitivity	2.7%	Common	0.0%
Investigations	Blood creatine phosphokinase increased	23.9%	Very common	5.1%
	Transaminases increased	16.4%	Very common	6.5%
	Gamma-glutamyltransferase increased	11.3%	Very common	6.7%
	Blood creatinine increased	9.4%	Common	0.8%
	Blood alkaline phosphatase increased	8.3%	Common	1.1%
	Lipase increased	7.8%	Common	4.3%

System Organ Class	Adverse drug reactions	Frequency (All grades)	Frequency Category (All grades)	Grade 3+
	Amylase increased	4.0%	Common	1.3%
Musculoskeletal and Connective Tissue Disorders	Myopathy/Muscular disorder	26.1%	Very common	1.3%
	Arthralgia	25.8%	Very common	0.8%
	Back pain	13.4%	Very common	0.8%
	Pain in extremity	11.0%	Very common	1.6%
	Rhabdomyolysis	0.3%	Uncommon	0.3%
Neoplasms benign, malignant and unspecified	Skin papilloma	6.5%	Common	0.0%
	Cutaneous squamous cell carcinoma	3.0%	Common	0.5%
	Basal cell carcinoma	0.8%	Uncommon	0.0%
Nervous System Disorders	Headache	18.8%	Very common	1.1%
	Dizziness	16.4%	Very common	2.2%
	Neuropathy	12.4%	Very common	1.1%
	Dysgeusia	7.0%	Common	0.0%
	Facial paresis	0.8%	Uncommon	0.3%
Renal and urinary disorders	Renal failure	3.5%	Common	1.9%
Skin and Subcutaneous Tissue Disorders	Rash	20.4%	Very common	1.1%
	Hyperkeratosis	16.4%	Very common	0.3%
	Dry skin	15.1%	Very common	0.0%
	Alopecia	14.0%	Very common	0.0%
	Pruritus	12.9%	Very common	0.3%
	Erythema	6.2%	Common	0.0%
	Palmar-plantar erythrodysaesthesia syndrome	5.1%	Common	0.0%
	Photosensitivity	4.3%	Common	0.3%
	Acneiform dermatitis	4.0%	Common	0.3%
	Panniculitis	1.1%	Common	0.0%
Vascular Disorders	Haemorrhage	16.7%	Very common	3.5%
	Hypertension	11.0%	Very common	5.1%
	Venous thromboembolism	4.8%	Common	0.8%

Percentages are based on number of subjects in Safety Set.
Frequency category: Very Rare < 0.01%; Rare [0.01% - 0.1%[; Uncommon [0.1% - 1%[; Common [1% - 10%[; Very Common >= 10%
MedDRA Version 25.1 has been used.
Version date: 31MAY2023

Selected adverse drug reactions description:

Table 43: Summary of Adverse Reactions and Associated Preferred Terms in the Combo 450 ISP

	Combo 450 ISP (N=372)						
						Outcome	
	Any Grade n(%)	Grade >=3 n(%)	Discontin. n(%)	Red/Int n(%)	Additional therapy n(%)	Rec/Res n(%)	Not Rec/Res n(%)
Vascular Disorders							
Haemorrhage	62 (16.7)	13 (3.5)	3 (0.8)	9 (2.4)	19 (5.1)	40 (10.8)	13 (3.5)
Hypertension	41 (11.0)	19 (5.1)	0 (0.0)	8 (2.2)	28 (7.5)	21 (5.6)	14 (3.8)
Venous thromboembolism	18 (4.8)	3 (0.8)	0 (0.0)	4 (1.1)	17 (4.6)	11 (3.0)	4 (1.1)
Gastrointestinal Disorders							
Abdominal pain	106 (28.5)	8 (2.2)	0 (0.0)	16 (4.3)	49 (13.2)	67 (18.0)	28 (7.5)
Colitis	12 (3.2)	5 (1.3)	1 (0.3)	6 (1.6)	9 (2.4)	10 (2.7)	2 (0.5)
Constipation	92 (24.7)	0 (0.0)	0 (0.0)	4 (1.1)	53 (14.2)	49 (13.2)	32 (8.6)
Diarrhoea	155 (41.7)	14 (3.8)	3 (0.8)	30 (8.1)	63 (16.9)	126 (33.9)	17 (4.6)
Nausea	171 (46.0)	11 (3.0)	3 (0.8)	36 (9.7)	99 (26.6)	119 (32.0)	41 (11.0)
Pancreatitis	3 (0.8)	3 (0.8)	0 (0.0)	1 (0.3)	2 (0.5)	3 (0.8)	0 (0.0)
Vomiting	116 (31.2)	7 (1.9)	2 (0.5)	26 (7.0)	36 (9.7)	101 (27.2)	9 (2.4)
Skin and Subcutaneous Tissue Disorders							
Acneiform dermatitis	15 (4.0)	1 (0.3)	0 (0.0)	2 (0.5)	7 (1.9)	11 (3.0)	2 (0.5)
Alopecia	52 (14.0)	0 (0.0)	0 (0.0)	1 (0.3)	7 (1.9)	15 (4.0)	27 (7.3)
Dry skin	56 (15.1)	0 (0.0)	0 (0.0)	1 (0.3)	20 (5.4)	19 (5.1)	26 (7.0)
Erythema	23 (6.2)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.9)	16 (4.3)	5 (1.3)
Hyperkeratosis	61 (16.4)	1 (0.3)	0 (0.0)	4 (1.1)	32 (8.6)	21 (5.6)	27 (7.3)
PPE syndrome	19 (5.1)	0 (0.0)	1 (0.3)	4 (1.1)	12 (3.2)	8 (2.2)	5 (1.3)
Photosensitivity	16 (4.3)	1 (0.3)	0 (0.0)	1 (0.3)	8 (2.2)	8 (2.2)	5 (1.3)
Pruritus	48 (12.9)	1 (0.3)	1 (0.3)	5 (1.3)	18 (4.8)	31 (8.3)	12 (3.2)
Rash	76 (20.4)	4 (1.1)	3 (0.8)	9 (2.4)	40 (10.8)	52 (14.0)	18 (4.8)
Nervous system Disorders							
Dizziness	61 (16.4)	8 (2.2)	1 (0.3)	7 (1.9)	6 (1.6)	38 (10.2)	18 (4.8)
Dysgeusia	26 (7.0)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.5)	11 (3.0)	11 (3.0)
Facial paresis	3 (0.8)	1 (0.3)	0 (0.0)	1 (0.3)	1 (0.3)	2 (0.5)	0 (0.0)
Headache	70 (18.8)	4 (1.1)	2 (0.5)	3 (0.8)	27 (7.3)	46 (12.4)	18 (4.8)
Neuropathy	46 (12.4)	4 (1.1)	0 (0.0)	3 (0.8)	9 (2.4)	19 (5.1)	23 (6.2)
Renal and urinary disorders							
Renal failure	13 (3.5)	7 (1.9)	1 (0.3)	6 (1.6)	8 (2.2)	10 (2.7)	1 (0.3)
Investigations							
Amylase increased	15 (4.0)	5 (1.3)	1 (0.3)	6 (1.6)	0 (0.0)	11 (3.0)	2 (0.5)
Blood alkaline phosphatase increased	31 (8.3)	4 (1.1)	1 (0.3)	10 (2.7)	0 (0.0)	27 (7.3)	1 (0.3)
Blood creatine phosphokinase increased	89 (23.9)	19 (5.1)	2 (0.5)	11 (3.0)	1 (0.3)	66 (17.7)	12 (3.2)
Blood creatinine increased	35 (9.4)	3 (0.8)	4 (1.1)	11 (3.0)	5 (1.3)	20 (5.4)	11 (3.0)
Gamma-glutamyltransferase increased	42 (11.3)	25 (6.7)	2 (0.5)	10 (2.7)	1 (0.3)	26 (7.0)	9 (2.4)
Lipase increased	29 (7.8)	16 (4.3)	1 (0.3)	11 (3.0)	0 (0.0)	23 (6.2)	1 (0.3)

	Combo 450 ISP (N=372)						
						Outcome	
	Any Grade n(%)	Grade >=3 n(%)	Discontin. n(%)	Red/Int n(%)	Additional therapy n(%)	Rec/Res n(%)	Not Rec/Res n(%)
Transaminases increased	61 (16.4)	24 (6.5)	5 (1.3)	25 (6.7)	5 (1.3)	45 (12.1)	7 (1.9)
Blood Disorders							
Anaemia	86 (23.1)	26 (7.0)	0 (0.0)	12 (3.2)	43 (11.6)	37 (9.9)	33 (8.9)
Neoplasms							
Basal cell carcinoma	3 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.5)	3 (0.8)	0 (0.0)
Cutaneous squamous cell carcinoma	11 (3.0)	2 (0.5)	0 (0.0)	1 (0.3)	6 (1.6)	10 (2.7)	1 (0.3)
Skin papilloma	24 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.2)	10 (2.7)	10 (2.7)
General Disorders and Administrative Site Conditions							
Fatigue	179 (48.1)	16 (4.3)	4 (1.1)	20 (5.4)	3 (0.8)	60 (16.1)	91 (24.5)
Peripheral oedema	64 (17.2)	4 (1.1)	0 (0.0)	2 (0.5)	16 (4.3)	32 (8.6)	23 (6.2)
Pyrexia	69 (18.5)	8 (2.2)	1 (0.3)	11 (3.0)	33 (8.9)	64 (17.2)	3 (0.8)
Eye disorders							
RPED	83 (22.3)	6 (1.6)	0 (0.0)	14 (3.8)	11(3.0)	48 (12.9)	16 (4.3)
Uveitis	13 (3.5)	1 (0.3)	0 (0.0)	7 (1.9)	12(3.2)	10(2.7)	2 (0.5)
Visual impairment	86 (23.1)	3 (0.8)	0 (0.0)	9(2.4)	5(1.3)	66(17.7)	13 (3.5)
Cardiovascular Disorders							
Left ventricular dysfunction (Cardiomyopathy)	35 (9.4)	5 (1.3)	3 (0.8)	23 (6.2)	7 (1.9)	25 (6.7)	8 (2.2)

N = number of participants in Safety Set; n = number of participants in analysis; Discontin: Discontinuation; Red/Int: Reduction/Interruption; Rec/Res: Recovered/Resolved.

Serious adverse event/deaths/other significant events

In the Combo 450 ISP, 40 (10.8%) on-treatment deaths were reported. Most on-treatment deaths were due to progression of the disease (32 deaths, 8.6%), AEs resulted in **on-treatment death** in 8 (2.2%) of participants). These AEs were myocardial infarction (NSCLC population), haemorrhage intracranial (NSCLC population), cerebral haemorrhage (Melanoma population), multiple organ dysfunction syndrome (Melanoma population), death (2 events, Melanoma population), euthanasia (Melanoma population) and committed suicide (Melanoma population).

The most common **SAEs** (≥ 2% of participants) were pneumonia and anaemia (2.2% each).

Laboratory findings

Haematology

In the Combo 450 ISP, anaemia was the most common newly occurring or worsening haematology abnormal value reported for 42.1% of participants (all grades), including 6.3% of participants with Grade 3 abnormal values (no Grade 4). Other common notable changes (reported

in ≥10% of participants) included lymphocyte count decreased in 23.1% of participants (all grades) with Grade 3 in 4.0% of participants (no Grade 4), leukocyte count decreased in 15.8% of participants (all grades), with no Grade ≥3; absolute neutrophil count decreased in 14.9% of participants (all grades), with 3.1% of participants with Grade ≥3 abnormal values and platelet count decreased in 14.0% of participants with 0.8% Grade ≥3 abnormal values. All other newly occurring or worsening haematology abnormal values (all grades) were reported in less than 10% of participants.

In Combo 450 ISP, the only haematology parameter that shifted from Grade ≤2 at baseline to Grade 3 post baseline in ≥5% of participants was anaemia (6.3%). No haematology parameters shifted from Grade ≤2 at baseline to Grade 4 post baseline except for 2 participants (0.5%) with neutrophil count decreased and 2 participants (0.5%) with platelet count decreased.

In the NSCLC population, as in the Melanoma population, anaemia was the most common newly occurring or worsening haematology abnormal value reported for 47.9% of participants (all grades), with 11.7% of participants reporting Grade 3 (no Grade 4). Common changes (reported in ≥10%participants) included lymphocyte count decreased in 25.6% of participants (all grades), with 5.3% of participants reporting Grade 3 (no Grade 4), platelet count decreased in 20.2% of participants with 1.1% Grade ≥3, absolute neutrophil and leukocyte counts decreased in 11.7% each (all grades) with respectively one participant (1.1%) and none experiencing Grade ≥3. All other newly occurring or worsening haematology abnormal values (all grades) were reported in less than 10% of participants.

In the NSCLC population, the most frequent haematology parameters that shifted from Grade ≤2 at baseline to Grade ≥3 post baseline (in ≥5% of participants) were anaemia (11.7%) and lymphocyte count decreased (5.3%), whereas in the Melanoma population no haematology parameters shifted from Grade ≤2 at baseline to Grade ≥3 post baseline in ≥5% of participants.

The only notable difference between NSCLC and Melanoma populations was incidence of Grade >=3 anaemia (11.7% vs 4.5% respectively). Other incidences of haematology abnormalities (all grades and Grade≥3 new occurrences or worsening under treatment) were comparable showing consistency between NSCLC population and COMBO 450 ISP.

Biochemistry

Some parameters were not tested at baseline in all populations, which makes the comparison between populations irrelevant for these tests.

- In Melanoma, lipase was not a mandatory test at baseline and further cycles.
- in NSCLC, GGT and CPK were not mandatory tests.

For the description of shifts from baseline to worst Grade, only parameters with > 50% participants with assessments at baseline are commented upon.

In the **Combo 450 ISP**, creatinine increase (93.7%), CPK increase (57.6%), and hepatic enzymes increases: GGT (47.9%, Melanoma population only), ALT (33.1%), AST (30.6%) and ALP (26.7%) were the most common newly occurring or worsening chemistry abnormalities (all grades). Other notable changes reported in ≥20% of participants for any CTCAE Grade were hyponatraemia (22.7%). The only chemistry parameters with newly occurring or worsening values of maximum Grade ≥3 reported for at least ≥5% were GGT increase (14.9%, Melanoma population only) and ALT increase (6.3%). **In the NSCLC population**, creatinine increase (90.5%), CPK increase (41.3%), and lipase increase (41.8%) were the most common newly occurring or worsening biochemistry changes. Other common notable changes reported in ≥20% for any CTCAE Grade

were ALT increase (34.0%), AST increase (30.9%), ALP increase (33.0%), hyperkalaemia (30.9%), hyponatraemia (26.6%), hypoalbuminaemia (35.1%), and amylase increase (21.7%). The biochemistry parameters with newly occurring or worsening values of maximum Grade ≥3 reported for at least ≥5% were lipase increase (15.4%), hyponatraemia (10.6%), AST increase (9.6%), ALT increase (8.5%) and CPK increase (5.4%).Notable differences between NSCLC and Melanoma populations were incidence of Grade ≥3 chemistry abnormalities (new occurrences or worsening under treatment) for hyponatraemia (10.6% vs 2.6% respectively) and AST increased (9.6% vs 3.0% respectively). Other incidences were comparable showing consistency in term of biochemistry assessments between NSCLC population and COMBO 450 ISP.

Urine analysis

Table 44: Newly occurring or Worsening Urinalysis Abnormalities Based on Worst CTC Grade [Safety Set]

	NSCLC (N=98) n/m (%)	Melanoma (N=274) n/m (%)	Combo 450 ISP (N=372) n/m (%)
Proteinuria [Urine Protein (High)]			
Grade 1		11/133 (8.3)	11/133 (8.3)
Grade 2		5/146 (3.4)	5/146 (3.4)
Grade 3		0/149	0/149
Grade 4		0/149	0/149

1/1

NSCLC is corresponding to PHAROS study; Melanoma is corresponding to Melanoma safety pool treated with encorafenib 450 mg QD and binimetinib 45 mg BID; N = number of participants in Safety Set; m= number of patients who had missing or less than grade x at baseline and with at least one post-baseline value for the lab parameter; n = number of patients who had missing or less than grade x at baseline, and worsened to grade x post-baseline; Combo 450 ISP is the pool of NSCLC and Melanoma populations.

Percentages are using m value as denominator.

Baseline is defined as the last non-missing value prior to the first dose of study treatment.

CTC grading version 4.03 is used.

Sources: W00090_NSCLC - Version date: 28JUN2023 9:00 - File Name: Sub3_1_6_c1_UrinAbnGr_saf_t.rtf

Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADLBCH:27JUN2023 ADSP1.ADSL:27JUN2023 - PGM Sub3_1_6_c1_UrinAbnGr_saf_t.sas 03MAY2023 16:41

Table 44 presents a summary of newly occurring or worsening proteinuria increased based on CTCAE Grade. Proteinuria was not assessed at each cycle in the NSCLC population; hence shifts are not interpretable. No Grade 3 or 4 abnormalities were observed in the Melanoma population.

Vital Signs

Vital signs (BP, pulse rate, body weight and body temperature) were measured at protocol-specified time points as a component of the safety monitoring.

Blood Pressure:

In the Combo 450 ISP post-baseline high systolic blood pressure (SBP) and diastolic blood pressure (DBP) values were reported in 62(16.9%) and 43 (11.7%) participants, respectively, and abnormal low SBP and DBP values were reported in 19 (5.2%) and 16 (4.4%) of participants, respectively.

In the NSCLC, post-baseline high SBP and DBP values were reported in 16 (16.7%) and 6 (6.3%) participants, respectively, and abnormal low SBP and DBP values were reported in 9 (9.4%) and 4 (4.2%) of participants, respectively.

Hypertension is a known risk for the combination of encorafenib and binimetinib.

Pulse rate:

In Combo 450 ISP 11 (3.0%) participants had post-baseline abnormal high pulse measurements, and 11 (3.0%) participants had abnormal low pulse measurements.

In NSCLC 8 (8.3%) participants had post-baseline abnormal high pulse measurements, and 2 (2.1%) participants had abnormal low pulse measurements. In the NSCLC population, newly occurring abnormal values reported for ≥10% participants included high temperature, low temperature, and high systolic blood pressure. In Combo 450 ISP newly occurring abnormal values reported for ≥10% participants included high temperature, low temperature, high systolic blood pressure, high diastolic blood pressure and high weight.

Electrocardiogram (Assessment of QTc Effects)

In the Combo 450 ISP, new QTcF > 500 ms was reported for 4 (1.1%) participants. An increase from baseline in QTcF of >60 msec was observed in 22 (6.0%) participants (including all participants with a new QTcF >500 msec). Nine (2.4%) participants had an all-causality AE of ECG QT prolonged.

In the NSCLC population, new QTcF > 500 ms was reported for 2 (2.1%) participants. An increase from baseline in QTcF of >60 msec was observed in 7 (7.3%) participants (including the 2 participants with a new QTcF >500 msec). Five (5.1%) participants had an all-causality AE of ECG QT prolonged.

Safety in special populations

Subpopulations defined for the reporting of AEs were

- age (<65 vs ≥65 years), <75 vs ≥75 years, <85 vs ≥85 years),
- gender and
- race (Caucasian vs Asian vs Other), and
- number of lines of prior therapy (1 vs 2 or more).

The following assessments are described in the Combo 450 ISP. Overall, no clinically relevant safety trends or differences were observed in these subpopulations in the NSCLC population, as compared to the Combo 450 ISP.

Age (< 65 years vs. ≥ 65 years; < 75 years vs. ≥ 75 years):

Overall, there was no clinically important effect of age on the safety of the combination of encorafenib and binimetinib.

In the Combo 450 ISP 230 (61.8%) participants were < 65 years, 107 (28.8%) participants were ⩾ 65 to < 75 years and 35 (9.4%) were ⩾ 75 years.

Participants aged ≥ 65 years vs < 65 years

In the Combo 450 ISP, the overall incidence of any AEs, AEs related to study treatment, AEs requiring additional therapy, SAEs, SAEs related to study treatment, and AEs leading to discontinuation of study treatment between the two age subgroups (<65 and ≥65 years) were similar. Adverse events requiring dose interruption of any study drug (59.8% vs 45.5%) were more frequently reported (≥10% absolute difference) in participants aged ≥65 years than in those aged <65 years.

When considering individual adverse events in the Combo 450 ISP, AEs reported more frequently (≥ 10% absolute difference in incidence) in one subpopulation vs the other were:

- in participants aged ≥ 65 years vs < 65 years: nausea (66.1% vs 44.4%), diarrhoea (56.5% vs 44.4%), vomiting (43.5% vs 33.3%), oedema peripheral (27.4%vs 11.1%), back pain (24.2% vs 13.9%), arthralgia (19.4% vs 8.3%), and abdominal pain upper and dysgeusia (each 12.9%vs 0%). All events of atrial fibrillation and QT prolongation occurred in participants over 65 years of age (46.5% each)
- in participants aged < 65 years vs. ≥ 65 years: none

In the Combo 450 ISP, the overall incidence of any ADRs, ADRs requiring additional therapy, ADRs requiring dose interruption of any study drug and ADRs leading to discontinuation of study treatment between the two age subgroups (<65 and ≥65 years) were similar.

When considering individual adverse reactions in the Combo 450 ISP, ADRs reported more frequently (≥ 10% absolute difference in incidence) in one subpopulation vs the other were:

- in participants aged ≥ 65 years vs < 65 years: diarrhoea (51.4% vs 35.7%), and pruritus (19.7% vs 8.7%),
- in participants aged < 65 years vs. ≥ 65 years: hyperkeratosis (20.9% vs 9.2%) and visual impairment (27.0 v 16.9%)

Participants aged ≥ 75 years vs < 75 years

The number of participants aged over 75 years old was low with respectively 20 and 15 participants in NSCLC and Melanoma population, however, as expected, the relative proportion of ≥75 years old participants was higher in the NSCLC population (20.4%) as compared to the Melanoma population (5.5%). Due to the limited number of participants aged ≥ 75 years in the Combo 450 ISP, comparisons between participants aged ≥75 years and those aged <75 years should be considered with caution.

In the Combo 450 ISP, Grade ≥3 AEs (77.1% vs 62%), SAEs (51.4% vs 40.1%), adverse events requiring dose modification of any study drug (77.1% vs 54.6%), AES leading to treatment discontinuation (34.3% vs 11.0%) were more frequently reported (≥10% absolute difference) in participants ≥75 years than those <75 years. Most common AEs occurring in participants over 75 years of age in the Combo 450 ISP were nausea (71.4%), diarrhoea (68.6%), vomiting (51.4%) fatigue (40.0%), asthenia (37.1%), anaemia (34.3%) and back pain (22.9%). AEs with higher incidence (risk differences ≥10%) in participants aged ≥75 years than were nausea, diarrhoea, vomiting, asthenia, anaemia, back pain, blood creatinine increased, and atrial fibrillation while alopecia, blood CK increased, dry skin, arthralgia and abdominal pain were AEs reported with higher incidence in participants aged <75 years (risk differences ≥10%).

In the Combo 450 ISP, the overall incidence of ADRs (all grades), serious ADRs and ADRs requiring additional therapy were similar between the two age subgroups (<75 and ≥75 years). Grade ≥3 ADRS (62.9% vs 45.7%), ADRs requiring dose modification of any study drug (60.0% vs 48.1%), ADRs leading to treatment discontinuation (25.7% vs 7.4%) were more frequently reported (≥10% absolute difference) in participants aged ≥75 years than in those aged <75 years.

When considering individual adverse reactions in the Combo 450 ISP, ADRs reported more frequently (≥ 10% absolute difference in incidence) in one subpopulation vs the other were as follows:

- in participants aged ≥ 75 years vs < 75 years: fatigue (74.3% vs 45.4%), nausea (71.4% vs 43.3), diarrhoea (68.6% vs 38.9%), vomiting (51.4% vs 29.1%), anaemia (34.3% vs 22.0%), blood creatinine increased (20.0% vs 8.3%) and back pain (22.9% vs 12.5%).
- in participants aged < 75 years vs. ≥ 75 years: arthralgia (27.0% vs 14.3%), myopathy/muscular disorders (27.3% vs 14.3%), hyperkeratosis (17.8% vs 2.9%), alopecia (15.4% vs 0%), blood creatine phosphokinase increased (25.5% vs 8.6%) and retinal pigment epithelial detachment (24.0% vs 5.7%).

Participants aged ≥ 85 years vs < 85 years

In the Combo 450 ISP, only 3 participants were aged ≥ 85 years. This number is considered not sufficient (≤ 20) to adequately assess differences in incidence of AEs as compared to the subpopulation of participants aged < 85 years (369 participants).

Race (Caucasian vs. Asian)

In the Combo 450 ISP, 347 (93.3%) participants were Caucasian, only 13 participants were Asian and 3 were Black or African American.

Gender (male vs female)

In Combo 450 ISP, 215 (57.8%) participants were males and 157 (42.2%) were females

The incidences of all-causality AEs (all grades and Grade≥3) were similar in male and female populations.

AEs (all grades) reported in more female participants than male participants (absolute difference ≥10%) included: nausea (59.9% vs 35.8%), diarrhoea (48.4% vs 36.7%) and vomiting (43.3% vs 22.3%) and alopecia (19.1% vs 9.3%),

No AEs (all grades) was reported in more male participants than female participants with an absolute difference ≥10% in incidence.

Renal impairment

Encorafenib undergoes minimal renal elimination. Therefore, no formal clinical study has been conducted to evaluate the effect of renal impairment on the PK of encorafenib and no additional clinical study dedicated to renal impairment has been conducted for encorafenib since the initial marketing authorisation.

As of the 22 January 2023 cut-off date, in the NSCLC population the overall incidences of adverse events (all grades) were similar in subgroups of participants with mild or moderate renal impairment or normal renal function (100%, 100% and 98.4%, respectively). The proportion of Grade≥3 events was higher in the mild (71.4%) and moderate renal impairment (100.0%) subgroups as compared to the normal function (65.6%) subgroup.

As of the 22 January 2023 cut-off date, in the Combo 450 ISP the overall incidence of adverse events (all grades) was similar in subgroups of participants with mild or moderate renal impairment or normal renal function (100%, 100% and 98.5%, respectively). The proportion of Grade≥3 AEs was higher in the mild (67.6%) and moderate renal impairment (85.7%) subgroups as compared to the normal function (59.8%) subgroup.

Hepatic Impairment

No new dedicated clinical study to evaluate the impact of hepatic impairment for encorafenib has been completed to expand on what has been reported in the initial marketing authorisation.

Safety related to drug-drug interactions and other interactions

No new data were submitted.

Discontinuation due to adverse events

In the PHAROS trial, reasons for discontinuation study treatment were listed as follows:

- In the treatment-naïve cohort: death (16 (27.1%) participants), withdrawal of consent (2 (3.4%) participants) and lost to follow up (1 (1.7%) participant)
- In the Previously treated cohort: death (13 (33.3%) participants), withdrawal of consent (5 (12.8%) participants) and other reason (1 (2.6%) participant)

For the proportion of AEs leading to discontinuation see Table 40 above.

Accordingly, the comparison of frequencies of AEs of any PT leading to discontinuation (NSCLC vs Melanoma) was 43.9% vs 40.1%. None of the PT lead in more than 5% to discontinuation of study treatment.

Post marketing experience

The post-marketing accumulated data remain in accordance with the previous cumulative experience from clinical trials and the safety information presented in the Product Information. Based on the evaluation of the cumulative safety data presented in the PBRERs and the benefit-risk analysis, the MAHs did not propose any safety-related changes to the reference safety information or changes to risk minimisation measures at the time of the last PBRER submission, which was found acceptable.

2.5.1. Discussion on clinical safety

Safety data from a total of 372 participants with BRAF V600 mutant advanced NSCLC (98 participants) or melanoma (274 participants) are presented to evaluate the combination of encorafenib 450 mg QD and binimetinib 45 mg BID with 50.3% of participants receiving ≥ 48 weeks of study treatment. The overall size of the safety dataset and the extent of exposure are sufficient to characterise the safety profile of encorafenib at the dose of 450 mg QD in combination with binimetinib 45 mg BID (COMBO 450).

The combination of encorafenib 450mg QD and binimetinib 45mg BID (Combo 450 ISP) was evaluated for the treatment of the serious and life-threatening- condition of advanced BRAF V600-mutant advanced NSCLC either in treatment-naïve patients or after prior failure of systemic therapy. This combination at the same doses and schedule of administration was initially approved in the EU on 20 September 2018 for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

The safety of Combo 450 was assessed in advanced NSCLC in the Phase 2 PHAROS study. Other studies supporting the safety assessment of Combo 450 are CMEK162B2301 [Part 1] (192 participants), CLGX818X2109 [Part A] (75 participants) and CMEK162X2110 (7 participants) and form the Melanoma population (274 participants) which was the basis for the first approval of encorafenib 450mg QD and binimetinib 45mg BID for the treatment of metastatic BRAF V600-mutant melanoma.

The Melanoma and NSCLC population were integrated to form the Combo 450 ISP (372 participants).

Demographic characteristics of Combo 450 ISP included some notable differences between the NSCLC and Melanoma populations. Participants in the NSCLC population were older (67.8 years [range 47.0-86.0 years], with 63.3% and 20.4% of participants aged ≥65 and ≥75 years respectively in the NSCLC population vs 56.0 years [range 20.0 -89.0 years], with 29.2% and 5.5% participants aged ≥65 and ≥75 years respectively in the Melanoma population). In addition, more females were enrolled in the NSCLC population (53.1% in the NSCLC vs 38.3% in the Melanoma population). At study entry 26.5% participants in the NSCLC population had an ECOG PS of 0 vs 72.3% in the Melanoma population. Consistent with a poorer performance status and an older median age in the NSCLC population, 75.5% of participants in the NSCLC population had a baseline cardiac risk vs 32.6% in the Melanoma population. In the NSCLC population, as compared to the Melanoma population, a higher percentage of participants had a history of cardiovascular disorders (notably atrial fibrillation 14.3% vs 3.3%), metabolic disorders (notably hyperlipidaemia 16.3% vs 3.2%), type 2 diabetes mellitus (13.3% vs 2.9%), respiratory disorders (chronic obstructive pulmonary disease - 19.4% vs 2.2%, dyspnoea - 38.8% vs 4.7%, cough - 27.6% vs 2.2%) reflecting differences in cancer type, age and risk factors for NSCLC vs Melanoma. All participants in the Melanoma population were previously untreated in the metastatic setting, whilst 39.8% participants in the NSCLC population were previously treated in the metastatic setting.

Differences in the periods of time when the studies included in Combo 450 ISP were conducted (before or during the COVID 19 pandemic) and differences in the monitoring of laboratory tests and of ophthalmic and dermatologic assessments may explain differences between the frequencies of some AEs in the NSCLC and the Melanoma populations.

Of note, encorafenib and binimetinib PK exposures were similar in participants with melanoma and NSCLC treated with encorafenib 450 mg QD in combination with binimetinib 45 mg BID.

In the Combo 450 ISP, the median duration of exposure to study treatment was 11.04 months

- 98.9% participants, experienced at least one AE with 63.7% Grade ≥3 AEs (51.1% Grade 3, 11.6% Grade 4 and 0.5% Grade 5)
- The incidence of on-treatment deaths (occurring during treatment or within 30 days of the last dose and including deaths due to progressive disease) was 10.8%. Most on-treatment deaths were due to disease progression.
- SAEs were reported in 41.1% of participants.
- AEs leading to treatment discontinuation occurred in 13.2% participants, AEs requiring dose reduction or interruption in 56.7%, whilst the incidence of AE requiring additional therapy was 90.9%.
- Nausea, diarrhoea, fatigue, vomiting, arthralgia, constipation, blood CK increased and anaemia were the most common AEs (>20% of participants).

In the NSCLC population at the 22 January 2023 cut-off date, the median duration of exposure to study treatment was 9.5 months.

- 99.0% participants, experienced at least one AE with 70.4% Grade ≥3 AEs (54.1% Grade 3, 12.2% Grade 4 and 2.0% Grade 5)
- The incidence of on-treatment deaths (occurring during treatment or within 30 days of the last dose and including deaths due to progressive disease) was 12.2% Most on-treatment deaths were due to disease progression.

- SAEs were reported in 43.9% of participants.
- AEs leading to treatment discontinuation occurred in 17.3% participants, AEs requiring dose reduction or dose interruption in 69.4 %, whilst the incidence of AE requiring additional therapy was 93.9%.
- Nausea, diarrhoea, fatigue, vomiting, anaemia, constipation, dyspnoea, pyrexia, oedema peripheral, vision blurred, and back pain were the most common AEs (>20% of participants).
- Overall, the pattern of AESIs in the NSCLC population is coherent with that observed in the first marketing application of encorafenib and binimetinib in the Melanoma population. Tachycardia was reported at a higher (> 5% more) incidence in NSCLC than Melanoma population but this is consistent with differences in baseline characteristics of the NSCLC and Melanoma populations.

The overall toxicity profile in terms of overall incidence of AEs, Grade ≥3 AEs and AEs leading to study drug discontinuation was generally similar in the NSCLC and Melanoma populations with the key differences being a higher frequency (≥ 10% difference in incidence) of dyspnoea, productive cough, hyponatraemia, nausea, diarrhoea, fatigue, vomiting, anaemia and lipase increased in the NSCLC than the Melanoma population, whilst arthralgia, blood CK increased, GGT increased, and headache were reported at a higher frequency (≥ 10% difference) in the Melanoma than the NSCLC population. These differences are aligned with differences in baseline characteristics of the populations (different indications and associated risk factors, different demographic characteristics e.g. median age, different baseline ECOG performance status) or differences in the monitoring of some laboratory parameters and in ophthalmic and dermatologic assessments between studies.

The overall safety profile in terms of overall incidence of AEs, Grade ≥3 AEs, SAEs and AEs leading to study drug discontinuation or drug modification was generally similar in the NSCLC population and in the Combo 450 ISP. Overall, Combo 450 ISP adequately reflects the safety profile observed in the NSCLC population. The absence of notable differences in the safety profile allows for the pooling of the safety data of the Melanoma and NSCLC populations.

ADRs occurred in 98.1% of participants in the Combo 450 ISP with 48.9% Grade ≥3 events. The most frequent ADRs were fatigue (48.1%), nausea (46.0%), diarrhoea (41.7%), vomiting (31.2%), abdominal pain (28.5%), myopathy/muscular disorder (26.1%) and arthralgia (25.8%).

When assessing the overall profile of ADRs of the Combo 450 ISP and their tolerability versus the known safety and tolerability profile of encorafenib 450mg QD and binimetinib 45 mg BID in the initial MAA in participants with BRAF V600 mutant melanoma to evaluate changes introduced by the NSCLC population, no relevant changes were observed, except for retinal pigment epithelial detachment, which incidence is 7.3% lower in the Combo 450 ISP than in the Melanoma population - potentially linked in a difference in the assessment of ocular toxicities between studies.

The safety profile of Combo 450 ISP does not markedly differ from the profile of encorafenib 450mg QD and binimetinib 45 mg BID previously reported in the initial MAA, in a population of melanoma patients. No new ADRs were identified. There is a single change in the frequency category of the previously reported ADRs, with basal cell carcinoma changing from common to uncommon (0.8% in Combo 450 ISP vs 1.1% in the Melanoma population).

Safety in special populations

Consistent with the initial marketing authorisation, no dose adjustment is recommended/required for subjects with mild or moderate renal impairment based on the population PK analysis and the comparable safety and tolerability observed between participants with mild or moderate renal

insufficiency and participants with normal renal function. A recommended dose has not been established for subjects with severe renal impairment. Encorafenib should be used with caution in these participants.

The existing recommendations for the administration of encorafenib remain unchanged in patients with mild hepatic impairment, and in the absence of sufficient clinical data, encorafenib is not recommended in participants with moderate or severe hepatic impairment (nor to binimetinib, by extension).

No dose adjustment is recommended/required with the Combo 450 ISP for participants aged > 65 years old. In patients aged > 75 years old, higher incidence of diarrhoea, nausea and asthenia were reported, these AE are commonly reported at higher incidence in patients aged 75-year-old and over as compared to younger patients, regardless of the type of therapy administered (Wildiers, 2020). Number of patients older than 85 years was too low (n=3) to draw conclusions on this specific subgroup.

In the Combo 450 ISP, 347 (93.3%) participants were Caucasian, only 13 participants were Asian and 3 were Black or African American. These numbers are considered very small and not sufficient to adequately assess differences in incidence of AEs as compared to the subpopulation of Caucasian participants.

No unexpected or new safety concerns were identified as compared to the known safety profile of encorafenib and binimetinib.

2.5.2. Conclusions on clinical safety

Integration of the PHAROS safety data (in NSCLC patients) into a pooled COMBO 450 ISP had remarkable few effects on this safety pool albeit the reminder of this pool consist in a malignant melanoma population (as of 3 different clinical trials). The NSCLC population is slightly older and had slightly more female patients.

The overall safety pool allows the inclusion of age-appropriate statements in the SmPC. Otherwise, only frequencies of known AEs have been slightly revised, and implemented appropriately in section 4.8 of the SmPC.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The WSA submitted updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.0 for Braftovi (encorafenib) is acceptable.

The PRAC considered that the risk management plan version 3.0 for Mektovi (binimetinib) is acceptable.

The CHMP endorsed the Risk Management Plans version 3.0 for Braftovi (encorafenib) and Mektovi (binimetinib) with the following content:

Safety concerns

Braftovi (encorafenib)

Table 45: Summary of the Safety Concerns for encorafenib

Summary of safety concerns	
Important identified risks	Secondary skin neoplasms: cuSCC and new primary melanoma
Important potential risks	QT prolongation Non-cutaneous malignancies with RAS mutation Over-exposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors Over-exposure in patients with moderate to severe hepatic impairment
Missing information	Use in patients with severe renal impairment

The summary of safety concerns for encorafenib is unchanged.

Considering the data in the safety specification, the safety concerns listed above are appropriate.

Mektovi (binimetinib)

Table 46: Summary of the Safety Concerns for binimetinib

Summary of safety concerns	
Important identified risks	Left ventricular dysfunction Haemorrhage Hepatotoxicity
Important potential risks	Pneumonitis/Interstitial lung disease
Missing information	None

The summary of safety concerns for binimetinib is unchanged.

Considering the data in the safety specification, the safety concerns listed above are appropriate.

Pharmacovigilance plan

Braftovi (encorafenib)

No routine pharmacovigilance activities beyond ADR reporting and signal detection are proposed.

No changes to the Pharmacovigilance plan were proposed by the MAH, which is acceptable, as no new safety concerns were identified as part of this procedure.

Mektovi (binimetinib)

Part III: no updates introduced.

Routine pharmacovigilance activities beyond ADR reporting and signal detection are proposed:

Specific AR follow-up forms, applicable to oncology, will be used as part of the routine pharmacovigilance activities to document and follow up any case of interest in relation to the safety concerns that will be covered by a list of surveillance terms for both – binimetinib and binimetinib-encorafenib combination.

Other forms of routine pharmacovigilance activities for safety concerns:

The following specific ARs follow up forms for binimetinib are provided in Annex 4:

- Left ventricular dysfunction
- Haemorrhage
- Hepatotoxicity
- Pneumonitis/Interstitial lung disease

No additional pharmacovigilance activities are necessary. Specific follow-up forms are included in Annex IV of the RMP.

Overall conclusions on the PhV Plan

Routine pharmacovigilance is sufficient to identify and characterise the risks of the products.

Risk minimisation measures

Braftovi (encorafenib)

Table 47: Summary table of pharmacovigilance activities and risk minimisation activities for safety concerns of encorafenib

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
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 sections 4.2 and 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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
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
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

Mektovi (binimetinib)

Table 48: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks for binimetinib in combination with encorafenib		
Left ventricular dysfunction	Routine: Dose modification recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PIL section. Listed in Section 4.8 of the SmPC and relevant PIL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products. Additional: none.	Routine: specific Left ventricular dysfunction ADR follow-up form. Additional: none
Haemorrhage	Routine: Dose modification recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PIL section. Listed in Section 4.8 of the SmPC and relevant PIL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products. Additional: none.	Routine: specific Haemorrhage ADR follow-up form. Additional: none.
Hepatotoxicity	Routine: Dose modification recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PIL section. Listed in Section 4.8 of the SmPC and relevant PIL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products. Additional: none	Routine: specific Hepatotoxicity ADR follow-up form. Additional: none

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risks for binimetinib in combination with encorafenib		
Pneumonitis/ Interstitial lung disease	Routine: Dose modification recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PIL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products. Additional: none.	Routine: specific Pneumonitis/ Interstitial lung disease ADR follow-up form. Additional: none.
Missing information for binimetinib in combination with encorafenib		
None		

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures for both Braftovi (encorafenib) and Mektovi (binimetinib) are sufficient to minimise the risks of the product in the proposed indication.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the Braftovi SmPC and sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the Mektovi SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the WSA and has been found acceptable as the changes are not considered to impact the readability of the PL.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Encorafenib in combination with binimetinib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600E mutation.

3.1.2. Available therapies and unmet medical need

According to the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) treatment guidelines 2023, the preferred first-line treatment for BRAF V600 mutated metastatic NSCLC in adults is the combination of dabrafenib and trametinib.

Single agent vemurafenib or dabrafenib are treatment options if the preferred combination is not tolerated. If participants progress on these targeted treatments, then systemic therapy (chemotherapy and/or immunotherapy) should be offered, and the type of therapy will vary depending on tumour histology type (ADC [non-squamous, or SCC).

3.1.3. Main clinical studies

The PHAROS trial is an uncontrolled, open-label phase 2 study to evaluate the safety, tolerability and antitumour activity of the combination of encorafenib and binimetinib in two parallel cohorts of treatment-naïve (planned number n=60, actually recruited n=59) and previously treated ((planned number n=37, actually recruited n=39) patients with BRAF V600-mutant NSCLC receiving encorafenib 450 mg QD and binimetinib 45 mg BID.

3.2. Favourable effects

Treatment-naïve patients (n=59)

Confirmed ORR (cORR) by independent radiology review (IRR) was 74.6% (95% CI: 61.6, 85.0), including 9 (15.3%) CRs and 35 (59.3%) PRs.

Median duration of response by investigator assessment was 40.0 months (95%CI: 23.1, NE).

Previously treated patients (n=39)

Confirmed ORR (cORR) by independent radiology review (IRR) was 46.2% (95% CI: 30.1, 62.8), including 4 (10.3%) CRs and 14 (35.9%) PRs.

Median duration of response by independent radiology review was 16.7 months (95%CI: 7.4, NE).

3.3. Uncertainties and limitations about favourable effects

The efficacy claims of COMBO 450 are based on a single pivotal uncontrolled open-label phase II study.

The exploratory nature of the study, with major protocol amendments and lack of confirmatory hypothesis testing, are major sources of uncertainty in the interpretation of the results, however, the magnitude of the observed ORR is sufficient to consider that there is evidence of antitumour activity.

Time to event endpoints such as OS and PFS cannot be contextualised in uncontrolled trials and the drug effect cannot be isolated.

3.4. Unfavourable effects

The safety of Combo 450 was assessed based on the Phase 2 PHAROS study. Other studies supporting the safety assessment of Combo 450 are CMEK162B2301 [Part 1] (192 participants), CLGX818X2109 [Part A] (75 participants) and CMEK162X2110 (7 participants) and form the Melanoma population (274 participants) which was the basis for the first approval of encorafenib 450mg QD and binimetinib 45mg BID for the treatment of metastatic BRAF V600-mutant melanoma.

The Melanoma and NSCLC population were integrated to form the Combo 450 ISP (372 participants).

ADRs occurred in 98.1% of participants in the Combo 450 ISP with 48.9% Grade ≥3 events. The most frequent ADRs were fatigue (48.1%), nausea (46.0%), diarrhoea (41.7%), vomiting (31.2%), abdominal pain (28.5%), myopathy/muscular disorder (26.1%) and arthralgia (25.8%).

The overall safety profile in terms of overall incidence of AEs, Grade ≥3 AEs, SAEs and AEs leading to study drug discontinuation or drug modification was generally similar in the NSCLC population and in the Combo 450 ISP. Overall, Combo 450 ISP adequately reflects the safety profile observed in the NSCLC population. The absence of notable differences in the safety profile allows for the pooling of the safety data of the Melanoma and NSCLC populations.

3.5. Uncertainties and limitations about unfavourable effects

N/A.

3.6. Effects Table

Table 49: Effects Table for Mektovi/Braftovi "for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation" (data cut-off: 22 Sep 2022)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Treatment-naïve population (n=59)						
cORR	Confirmed response by IRR	%	74.6 (95%CI: 61.6, 85.0)	N/A	Uncontrolled open-label study	CSR
DoR	Duration of Response by IRR	months	40.0 (95%CI: 23.1, NE)			
Previously treated population (n=37)						
cORR	Confirmed response by IRR	%	46.2 (95%CI: 30.1, 62.8)	N/A	Uncontrolled open-label study	CSR
DoR	Duration of Response by IRR	months	16.7 (95%CI: 16.7, NE)			
Unfavourable Effects Overall safety population (n=98)						
AEs related	All grades related	%	93.9%	N/A	Uncontrolled, small sizes safety population	
≥ 3 AEs, related	grade ≥ 3, related	%	44.9		Uncontrolled, small sizes safety population	
AEs leading to treatment	All grades, related and unrelated	%	17.3	N/A	Uncontrolled, small sizes safety	SCS

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
discontinuation					population	
AEs requiring treatment dose interruption and/or dose adjustment	All grades, related and unrelated	%	69.4.3		Uncontrolled, small sizes safety population	SCS

Abbreviations: CSR = Clinical Study Report; INV = investigator-assessed; IRR = independent radiological review; SCS = Summary of Clinical Safety

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Favourable effects

Treatment-naïve subpopulation

Reported cORR (IRR and INV) are an indicator of substantial clinical activity. The effect size is in a comparable range and similar to dabrafenib/trametinib being the current standard of care for patients with metastatic NSCLC harbouring BRAF V600E point mutations. Duration of response is still immature, magnitude of activity appears to be at least not lower than reported for dabrafenib/trametinib.

Previously treated subpopulation

Reported cORR (IRR and INV) are an indicator of clinical activity. The effect size is lower compared to the 'treatment-naïve' cohort of the PHAROS trial, and also compared to the 'previously treated' cohort of dabrafenib/trametinib study BRF113928, currently being the standard of care for patients with advanced NSCLC harbouring BRAF V600 point mutations. However, the effect size is considered sufficient to substantiate clinical activity.

Indication

In the absence of any recruited patient expressing single amino-acid changes else than V600E (only 1 patient with BRAF-V600D in addition to V600E included in PHAROS) and in line with the biomarker-positive definition for eligibility in the PHAROS study, which is "any short variant with protein effect V600E as detected by F1CDx and F1LCDx", it is unknown whether the favourable treatment effects observed in BRAF-V600E patients could be extrapolated to a non-V600E (any V600) population. Accordingly, the B/R is only considered positive for V600E mutations and the final indication wording was revised accordingly.

Unfavourable effects

Almost all patients experienced ADRs and nearly 50% experienced ADRs Grade ≥3 events.

The ISS as well as the COMBO450 ISP (integrated safety population) confirm that the safety profile of COMBO450 is approximately the same in melanoma and NSCLC patients, thus established, manageable, and acceptable.

3.7.2. Balance of benefits and risks

The reported ORR in combination with (immature) DoR outweigh the manageable and acceptable risk of COMBO 450 for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600E mutation.

3.7.3. Additional considerations on the benefit-risk balance

None

3.8. Conclusions

The overall B/R of Braftovi and Mektovi is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include binimetinib in combination with encorafenib for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600E mutation for MEKTOVI and BRAFTOVI based on results from study PHAROS (Study ARRAY-818-202) at the primary completion date; this is a Phase II, open-label, multicentre, non-comparative study (interventional). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the Braftovi SmPC and sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the Mektovi SmPC are updated. The Package Leaflet is updated in accordance. Version 3.0 of Braftovi and Mektovi RMPs have also been approved.

The worksharing procedure leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Additional market protection

The request for one year of market protection for a new indication for Mektovi was withdrawn by the MAH during the current procedure.