RISK MANAGEMENT PLAN

Binimetinib

Active substance(s) (INN or common name):	Binimetinib
Pharmaco-therapeutic group (ATC Code):	Antineoplastic agent, protein kinase inhibitor. ATC code: L01EE03
Name of Marketing Authorisation Holder or Applicant:	Pierre Fabre Médicament
Names of medicinal products to which this RMP refers:	Binimetinib
Product concerned (brand name):	MEKTOVI

RMP version to be assessed as part of this application:

RMP version number:	3.0
Data lock point for this RMP:	26 June 2023
Date of final sign off:	06 August 2024
Submission date:	11 October 2023
Procedure number:	EMEA/H/C/004579/WS2538/0030
Rationale for submitting an updated RMP:	Variation Type II – New indication

Summary of significant changes in this RMP:

Parts	Modules	Changes
Part I	Product Overview	Addition of information relevant to the new indication Removal of the product from the EU additional monitoring list following five years of authorisation (Procedure no: EMEA/H/C/004579/R/0024) ATC code updated
Part II	SI, SIV	Addition of information relevant to the new indication
	SII	Information was added to the non-clinical findings for binimetinib single agent regarding: - Repeat dose toxicity, adding information about the mixed cell infiltrates in the parenchyma of the liver; - Fertility, adding precise wording about the absence of toxicological observation in reproductive organs of rats and monkeys of either sex in repeat-dose toxicity studies. The added information does not come from new non-clinical data and does not impact the list of safety concerns. This information was added to this RMP version to document more precisely the initially reported non-clinical results.
	SIII	Updated taking in consideration the addition of new indication population. Update the cut off dates of studies for melanoma indication.
	SV	Update of the post-authorisation experience as of the DLP
	SVII	Update taking into consideration: the population of the new indication, and the updated cut off dates of studies for melanoma population Addition of post-authorisation data
Part VI	-	Updated according to changes in other parts
Part VII	-	Annex 4 updated with the new versions of Specific adverse drug reaction follow-up forms Annex 7 and Annex 8 Updated according to changes in other parts

Other RMP Versions under Evaluation:

None

Details of the Currently Approved RMP:

Version number:	2.0
Approved with procedure:	EMEA/H/C/004579/IB/0009
Date of approval:	24 April 2020

EU QPPV name: Isabelle GEORGE

EU QPPV signature: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s EU QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

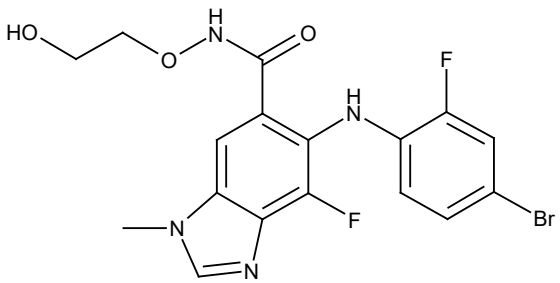
Abbreviation	Definition
ADME	Absorption, Distribution, Metabolism and Excretion
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ASR	Age-Standardized incidence Rate
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATP	Adenosine Triphosphate
AUC	Area Under the Curve
AUC_{ss}	Area Under the Curve at Steady State
BCRP	Breast Cancer Resistance Protein
BID	Twice Daily
Bini 45 P	Binimetinib 45 mg Population
BP	Blood Pressure
BRAF	B-Raf Proto-Oncogene, Serine/Threonine Kinase
CI	Confidence Interval
CK	Creatine Phosphokinase
C_{max}	Maximum Concentration
$C_{max,ss}$	Maximum Concentration at Steady State
$C_{min,ss}$	Trough Concentration at Steady State
Combo BP	Combination (binimetinib + encorafenib) Broad Population
Combo 450 RP	Combination (binimetinib + encorafenib) 450 mg Restricted Population
CNS	Central Nervous System
CrCL	Calculated Creatinine Clearance
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiac Ventricular Dysfunction
CYP	Cytochrome P 450
EAIR	Exposure-Adjusted Incidence Rate
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERK	Extracellular Signal-Regulated Kinase
ESMO	European Society for Medical Oncology
EU	European Union
EUCAN	European Cancer Observatory
GGT	Gamma-Glutamyltransferase
HCP	Health Care Professional
hERG	Human Ether-A-Go-Go-Related Gene
HIV	Human Immunodeficiency Virus
HR	Heart Rate

IB	Investigator's Brochure
IC50	Half Maximal Inhibitory Concentration
ICH	International Council for Harmonization
INN	International Non-proprietary Name
INR	International Normalised Ratio
ISP	Integrated Safety population
ISS	Integrated Summary of Safety
ILD	Interstitial Lung Disease
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MAA	Marketing Authorisation Application
MAPK	Mitogen Activated Protein Kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-Activated Protein Kinase Kinase
mRNA	Messenger RNA
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NRAS	Neuroblastoma Ras Viral (V-Ras) Oncogene Homolog
NSCLC	Non-Small Cell Lung Cancer
OATP	Organic Anion Transporting Polypeptide
OCT	Organic Cation Transporter
OS	Overall Survival
PBRER	Periodic Benefit-Risk Evaluation Report
PIL	Patient Information Leaflet
P-gp	P-Glycoprotein
PI3K	Phosphatidylinositol 3-Kinase
PK	Pharmacokinetic(s)
PRAC	Pharmacovilance Risk assessement Committee
PS	Performance Status
PSUR	Periodic Safety Update Report
PT	Preferred Term
QD	Once Daily
QoL	Quality of life
QPPV	Qualified Person Responsible for Pharmacovigilance
QT	QT-Interval On ECG
QTc	Rate-Corrected QT Interval
QTcF	QT Interval Corrected for Heart Rate Using Fridericia's Formula
RAF	Rapidly Accelerated Fibrosarcoma
RAS	Rat Sarcoma
RMP	Risk Management Plan
RPED	Retinal Pigment Epithelial Detachment
RR	Relative Risk
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SCC	Squamous Cell Carcinoma
SmPC	Summary of Product Characteristics
SOC	System Organ Class

SSM	Superficially Spreading Melanoma
TKI	Tyrosine Kinase Inhibitor
UGT	Uridine 5'-Diphospho-Glucuronosyltransferase
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
VTE	Venous Thromboembolism
WHO	World Health Organization
wt	Wild Type

PART I: PRODUCT OVERVIEW

Table Part I.1: Product Overview

Active substance(s) (INN or common name)	Binimetinib
Pharmaco-therapeutic group (ATC Code)	Antineoplastic agent, protein kinase inhibitor ATC code: L01EE03
Name of Marketing Authorisation Holder or Applicant	Pierre Fabre Médicament
Names of medicinal products to which this RMP refers	Binimetinib
Invented name(s) in the European Economic Area (EEA)	MEKTOVI
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class** Binimetinib is an antineoplastic agent, selective, small molecule ATP-uncompetitive inhibitor of mitogen-activated protein (MAP) kinase (MEK) 1 and 2.
	Structural formula  **Molecular formula** $C_{17}H_{15}BrF_2N_4O_3$
	Summary of mode of action Binimetinib is an orally available, ATP-uncompetitive, reversible inhibitor of MEK1 and MEK2 activation. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. In vitro, binimetinib potently inhibits MEK dependent phosphorylation of ERK in human N-Ras and B-Raf mutant melanoma cell lines; significantly inhibiting proliferation and viability of these cell lines. In vivo, binimetinib has been evaluated for its ability to inhibit phosphorylation of ERK and tumour growth in numerous xenograft models in nude mice. Binimetinib has shown potent anti-tumour activity in numerous BRAF-mutant xenograft models, including melanoma and non-small cell lung cancer (NSCLC). Overall, binimetinib has demonstrated

	potent activity against MEK1/2 enzymes and possesses broad anti-proliferative activity in vitro and in vivo.
	Important information about its composition Each film-coated tablet contains 15 mg of binimetinib. The tablets are yellow to dark yellow and capsule shaped. Excipients: Tablet core: lactose monohydrate, microcrystalline cellulose (E460i), colloidal silicon dioxide (E551), croscarmellose sodium (E468), and magnesium stearate (vegetable source) (E470b). Coating: polyvinyl alcohol (E1203), Macrogol 3350 (E1521), titanium dioxide (E171), talc (E533b), iron oxide yellow (E172), iron oxide black (E172). Excipients with known effect: each film coated tablet contains 133.5 mg of lactose monohydrate.
Hyperlink to the Product Information:	Summary of Product Characteristics MEKTOVI
Indication(s) in the EEA	**Current:** Binimetinib is indicated for use in combination with encorafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. **Proposed:** <u>Melanoma</u> Binimetinib in combination with encorafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation, <u>Non-small cell lung cancer (NSCLC)</u> Binimetinib in combination with encorafenib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600E mutation.
Dosage in the EEA	**Current:** In unresectable or metastatic melanoma with a BRAF V600 mutation, the recommended dosage regimen of binimetinib is 45 mg (3 tablets of 15 mg) orally taken twice daily (BID), approximately 12 hours apart. Treatment with binimetinib in combination with encorafenib should continue until the patient experiences disease progression or development of unacceptable toxicity. If a dose of binimetinib is missed, it should not be taken within 6 hours of the next dose of binimetinib. In case of vomiting after administration of binimetinib, the patient should not take an additional dose of the medicinal product and should resume dosing with the next scheduled dose. Binimetinib tablets are to be swallowed whole with water and may be taken with or without food.

	Proposed: In unresectable or metastatic melanoma with a BRAF V600 mutation, and in advanced non-small cell lung cancer (NSCLC) with a BRAF V600E mutation, the recommended dose of binimetinib is 45 mg (3 tablets of 15 mg) twice daily (BID), corresponding to a total daily dose of 90 mg, approximately 12 hours apart. Treatment with binimetinib in combination with encorafenib should continue until the patient no longer derives benefit or the development of unacceptable toxicity. If a dose of binimetinib is missed, it should not be taken if it is less than 6 hours until the next dose is due. In case of vomiting after administration of binimetinib, the patient should not re-take the dose and should take the next scheduled dose. Binimetinib tablets are to be swallowed whole with water and may be taken with or without food.
Pharmaceutical form(s) and strengths	**Current:** Film-coated tablets for oral administration. Each tablet contains 15 mg binimetinib.
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

At the time of this RMP, no indication is intended for the use of binimetinib as monotherapy.

In the current therapeutic use, binimetinib (MEKTOVI) is indicated in combination with encorafenib (BRAFTOVI) for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600E mutation.

The safety of binimetinib (45 mg orally twice daily) in combination with encorafenib (450 mg orally once daily) was evaluated in 274 patients (Combo 450 RP population; also referred to as 'Melanoma population' in this RMP) with BRAF V600 mutation-positive unresectable or metastatic melanoma, based on two phase II studies (CMEK162X2110 and CLG818X2109) and the pivotal phase III study (CMEK162B2301).

In the newly proposed therapeutic use, binimetinib is indicated, in combination with encorafenib, for the treatment of adult patients with advanced NSCLC with a BRAF V600E mutation. In this indication, the safety of binimetinib (45 mg orally twice daily) in combination with encorafenib (450 mg orally once daily) was evaluated in 98 patients with BRAF V600E mutant advanced NSCLC enrolled and treated in the PHAROS study (C4221008, ARRAY 818-202). Binimetinib 45 mg orally BID in combination with encorafenib 450 mg orally QD is the same dosage and administration schedule as the one recommended in the melanoma indication. The analysis of safety data pertaining to binimetinib in combination with encorafenib in the proposed indication (advanced BRAF V600E mutant NSCLC) did not identify any new safety concern of binimetinib as compared to the known safety concerns already included in the RMP.

Part II: Module SI - Epidemiology of the Indication(s) and Target Population

- **Indication: treatment of adult patients with BRAF V600 mutation unresectable or metastatic melanoma**

Incidence:

EUCAN data from 2012 indicate an age-standardised incidence rate of malignant melanoma of the skin in the EU of 13.0 per 100,000 of population per year, with Switzerland (25.8/100,000), the Scandinavian nations of Norway (25.3/100,000), the Netherlands (24.4/100,000), Denmark (24.1/100,000) and Sweden (23.9/100,000) reporting the highest rates amongst all European nations (European Cancer Information System; Steglich 2018). Given that there are currently 508 million individuals living in the EU (European Commission), and assuming that 20% of diagnosed melanomas progress to a metastatic stage, and that approximately 50% of these cases are positive for BRAF V600E mutations (Ascierto 2012), approximately 6,552 individuals per year will be diagnosed with BRAF V600E-mutated stage IV metastatic melanoma in Europe.

Prevalence:

The frequency of BRAF-positive mutations in patients with metastatic melanoma has been reported in several recent real-world studies conducted in the EU, ranging from as low as 29% to as high as approximately 62% (Lyons 2016; Rutkowski 2014), with the variability likely due to varying sample sizes. One large study of 2,532 patients with unresectable stage IIIB–IV melanoma from France, Germany, Italy, Spain and the United Kingdom (UK) identified 50% of patients with BRAF-mutated disease (Burudpakdee 2016). Though the incidence of melanoma is higher in countries such as Switzerland and the Scandinavian nations, real-world studies conducted in these countries have reported frequencies of BRAF-mutated disease amongst cutaneous melanoma patients of approximately 51–54% (Edlundh-Rose 2006; Frauchiger 2016), similar to rates reported for other European nations. Among the subtypes of BRAF V600-mutation positive melanomas, the V600E mutation predominates, with recent real-world studies reporting frequencies of approximately 65% to 92% (Rutkowski 2014; Heinzerling 2013) suggesting that these mutations represent upwards of 37% of all metastatic cutaneous melanoma cases in Europe (Heinzerling 2013). Similar to BRAF mutations overall, these studies suggest that countries with high melanoma incidence do not differ in terms of V600E mutation rates (Edlundh-Rose 2006).

Demographics of the target population with unresectable, BRAF-mutated metastatic melanoma and risk factors for the disease:

Interestingly, the sex distribution of the incidence of malignant melanoma can vary by geographical region, with some higher-latitude populations such as Scotland and Canada historically reporting higher incidence in women than men, in contrast to other mid- or low-latitude populations, such as Australia and the US, which report higher incidence in men (Nardin 2015). EUCAN 2012 data report incidence rates of 11.4/100,000 and 11.0/100,000 in men and women, respectively, suggesting that in European populations, malignant melanoma occurs roughly equally amongst the sexes. This trend appears to be supported by real-world studies in Europe with regard to the distribution of BRAF-mutated disease as well, with one Polish study finding an approximately equal distribution of BRAF-mutated stage IIIC or IV metastatic melanoma between men (51%, 78/154) and women (49%, 76/154) (Rutkowski 2014). Conversely, a small French study reported up to 66% (23/35) of male patients with stage III BRAF-mutated disease, though the sex distribution of patients with wildtype BRAF was similar, suggesting that the frequency of BRAF mutation status is unlikely to differ by sex from the overall frequency of melanoma, although this should be interpreted with caution given the small sample size (Schlaak 2013). In addition, these patterns do not appear to differ in European countries with high melanoma incidence (Edlundh-Rose 2006; Frauchiger 2016).

The age at diagnosis of BRAF-mutated melanoma appears to differ from those patients with wildtype BRAF melanoma, with BRAF mutation-positive patients often significantly younger at diagnosis. European real-world studies have reported median ages at diagnosis of approximately 50 to 59 years (Frauchiger 2016; Colombino 2013), in contrast to patients with wildtype BRAF disease, whose median age at diagnosis is reported from 62 to 66 years (Frauchiger 2016; Colombino 2013). Among patients with V600-mutated disease, reports have shown that approximately 31% of patients are diagnosed at <50 years of age, while only 15% of wildtype BRAF disease is diagnosed in this age range (Whiteman 2011). One German study of 141 patients with metastatic melanoma specifically examined associations of patient characteristics with BRAF mutation status and found that younger age correlated strongly with the risk of developing BRAF V600E mutated melanoma (Picard 2014), supporting previous findings reported in US populations (Moreau 2012).

Previously published reports conducted in the US have shown that ethnic origin may affect the incidence of cutaneous melanoma, as the incidence of the disease in Caucasians is much higher than observed in people classified as Hispanic, African-American, American Indian, or Asian (Meckbach 2014). Meta-analyses have also shown that patients with red or blond hair, blue eyes, fair skin, and those who easily develop sunburn are at higher risk for melanoma than subjects with darker hair and eyes, and skin that tans easily (Thomas 2007). To our knowledge, there are no reports in European populations of associations of ethnicity or race with BRAF V600-mutated melanoma, so specific demographic characteristics associated with this mutation are currently unknown.

The existing literature has suggested a complex relationship between UV exposure and the risk of BRAF V600E mutation-positive melanoma (Moreau 2012). An Australian study of 251 patients reported several factors that appeared to be associated with BRAF V600E mutations in melanoma, including fewer freckles (ephelides), high self-reported childhood levels of sun exposure, and more frequent pigment production in the tumour (Cornier 2006). Australian studies have also suggested that BRAF V600E-positive melanoma more frequently appeared on the trunk and distal extremities than on the head and neck, in contrast to wildtype BRAF melanoma, which appeared more frequently on the head and neck than on the trunk or extremities (Cornier 2006). The former findings are supported by the Swiss study reported by Frauchiger *et a*l, where BRAF-mutated melanoma appeared most frequently on the trunk (43%), while only 16% of patients had tumours in the head and neck area, in comparison with wildtype BRAF which appeared with similar frequency on the trunk (22%) and head/neck (17%) (Frauchiger 2016). A Swedish study reported a similar finding, wherein primary tumours on the trunk were more likely to harbour BRAF-mutations (58%) than wildtype tumours (18%) (Edlundh-Rose 2006). Two other real-world European reports have found similar rates of primary tumour site on the trunk and head/neck area (Rutkowski 2014; Colombino 2013), or indeed the opposite effect, wherein a higher frequency of BRAF wildtype primary tumours were reported on the trunk (Schlaak 2013). The German Schlaak *et al*. study specifically analysed clinical parameters associated with the development of BRAF V600-mutated melanoma and found that mutated melanomas preferentially developed on areas of intermittent sun exposure such as the trunk, and that patients with more melanocytic naevi were also more likely to develop BRAF-mutated disease (Picard 2014), a finding concordant with previous findings in US populations (Moreau 2012). Interestingly, Schlaak *et al.* did not find associations of total sun burden score, use of tanning beds, sunburn or skin type with BRAF mutation status. Nevertheless, theories of divergent pathogenesis and clinical characteristics of BRAF V600E-positive and wildtype BRAF melanomas have been suggested in the literature (Gandini 2005).

<u>The main existing treatment options:</u>

The BRAF inhibitors vemurafenib and dabrafenib and MEK inhibitors trametinib and cobimetinib are currently approved by the EMA for the treatment of BRAF-mutated melanoma. Consensus guidelines issued by European bodies state that treatment with a combination of BRAF and MEK inhibitors is the current standard of care in patients with BRAF V600E mutation-positive metastatic melanoma and recommends these therapies as first or second-line treatment (Liu 2007). Burudpakdee *et al*. examined real-world treatment patterns from Q2 2014 to Q1 2015 of patients with unresectable stage IV metastatic melanoma from France, Germany, Italy, Spain and the UK, and found vemurafenib to be the most common first-line therapy in patients with BRAF-mutated tumours

(France: 61.4%, Germany 56.3%, Italy: 75.0%, Spain: 52.8%, UK: 84.6%). As secondline therapy, the study found that ipilimumab was the most frequently used agent in these countries, regardless of BRAF mutation status (Burudpakdee 2016).

Cutaneous side effects are of concern in the treatment of BRAF-mutated metastatic melanoma (Bauer 2011). Treatment with combination BRAF and MEK inhibitors is known to have a slightly different profile of cutaneous side effects than BRAF inhibitors in single agent. A retrospective real-world study conducted in Australian patients treated with combination dabrafenib and trametinib (CombiDT) appeared to have a higher frequency of folliculitis (40%), but a lower frequency of cutaneous squamous cell carcinoma (26.1% with dabrafenib single agent versus 0% in CombiDT) and other squamo-proliferative disorders (Garbe 2016). Smaller real-world studies conducted in Europe have reported varying rates of squamous cell carcinoma (SCC) and squamo6proliferative disorders in BRAF single agent, from approximately 5% (2/40) for basal cell carcinoma with dabrafenib single agent (Welsh 2015) and 8% (1/13) for SCC with vemurafenib single agent (Carlos 2015), to as little as 0% (0/376) SCC for vemurafenib + cobimetinib (Cocorocchio 2016). Other severe skin toxicities have also been reported in European real-world studies, with grade 3/4 rash ranging from 0% (0/48) with CombiDT in Italy to 18% (12/65) with vemurafenib in one Slovenian study (Goppner 2014; Meyer 2016).

Natural history of BRAF mutated metastatic melanoma in the population, including mortality and morbidity:

EUCAN data from 2012 indicate overall mortality rates from cutaneous melanoma of 2.3/100,000 in Europe, with the highest rates seen in Norway (5.1/100,000), Slovenia (4.4/100,000), Sweden (4.0/100,000), the Netherlands (3.9/100,000) and Iceland (3.6/100.000) (European Cancer Information System). A German study reported a one-year OS rate of 44% (95% CI: 33.1, 53.9) amongst BRAF V600E mutation-positive patients treated with non-targeted therapies such as dacarbazine and temozolomide, and found no prognostic value of BRAF status, age or gender in these patients (Whitemann 2011). The Swiss Frauchiger *et al*. study of patients with stage IV metastatic melanoma found a median OS of 9.2 months (95% CI: 6.9–11.3 months) in patients with BRAF-mutated disease, which was not significantly different from the median OS of 10.6 months (95% CI: 9.1–12.2 months, p=0.25) in patients with wildtype BRAF disease (Frauchiger 2016). These results were supported by the Schlaak *et al*. study conducted in Germany, which enrolled patients with stage III disease and found that once patients progressed to stage IV, median OS was not influenced by BRAF status (BRAF-mutated: 8.5 months, n=22; wildtype BRAF: 8.0 months, n=20) (Picard 2014). Interestingly, another German study by Heinzerling *et al*. found that stage IV patients with BRAF V600E-mutated disease reported longer median OS (18 months, n=21) versus wildtype BRAF disease (13.5 months, n=20), although this effect was not statistically significant (p=0.695) (Heinzerling 2013).

The Swiss Frauchiger *et al*. study also examined clinical characteristics associated with OS, and found that elevated levels of lactate dehydrogenase (LDH) had a negative impact on median OS, both in BRAF-mutated tumours (elevated LDH: 6.95 months [95% CI: 5.6–9.5 months], normal LDH: 14.2 months [95% CI: 11.2–17.3 months], p=0.01) and patients with wildtype BRAF disease (elevated LDH: 4.9 months [95% CI: 3.5–6.2 months], normal LDH: 10.7 months [95% CI: 8.512.8 months], p<0.01) (Frauchiger 2016).

Analyses of differing patient characteristics between those with BRAF-mutated and wildtype BRAF disease showed a difference in the clinical subtypes of melanoma, wherein fewer patients with wildtype BRAF had nodular (NM) (31%, 21/67) and superficial spreading melanoma (SSM) (12%, 8/67) than patients with BRAF-mutated disease (NM: 36%, 32/88; SSM: 20%, 18/88) (Frauchiger 2016). Nevertheless, the study supports previously published reports of stage IV melanoma characteristics in general, in that NM and SSM remain the most common subtypes of advanced melanoma regardless of BRAF status (Frauchiger 2016; Cavalieri 2016).

Important co-morbidities:

The impact of comorbidities is poorly studied in melanoma, and there are no known common comorbidities associated with the cancer. One large Danish registry-based study which included 23,476 patients diagnosed with melanoma between 1987 and 2009, identified that 81% of patients did not have comorbidities (Ocvirk 2016). Of those who did have comorbidities, the most common were cancer (excluding melanoma and non-melanoma skin cancers) at 3.9% (915/23,476) of patients, cerebrovascular disease (3.4%, 739/23,476) and chronic pulmonary disease (2.4%, 558/23,476) (Ocvirk 2016). The study found that standardised mortality rates increased with increasing comorbidity, with interaction effects found between melanoma and comorbidity on mortality rates in the first year after diagnosis, though these effects became less pronounced after the first year if the patient survived (Ocvirk 2016). Stratifying by melanoma stage, the study reported that the interaction effects were concentrated in patients with distant metastases (Ocvirk 2016). Despite the potential importance of these findings, we are unaware of any studies examining the specific comorbidities of BRAF V600E-positive disease.

- **Indication: treatment of adult patients with advanced Non-Small Cell Lung Cancer (NSCLC) with a BRAF V600E mutation**

Incidence and prevalence:

Lung cancer is the second cancer in terms of new cases and is the leading cause of cancer death worldwide. Globally, in 2020, the age-standardized incidence rates (ASRs) for all stages of lung cancer have been estimated to be 31.5 and 14.6 per 100,000 population per year in men and women respectively. This was estimated to equal approximately 2,21 million new cases in 2020 – 1,435,943 in men and 770,828 in women (Sung, 2021).

In European countries Non-small cell lung cancer is the second most common type of cancer accounted for 11.8% of all new cancer diagnoses (excluding non-melanoma skin cancer) with an incidence of about 477,500 new cases (315 100 in men and 162 500 in women) in 2020 (Dyba, 2021). For males, incidence was highest in Central and Eastern Europe–Hungary (138.3 per 100,000), Serbia (136.4), Bosnia and Herzegovina (131.3), and Latvia (127.9), and in some countries of Southern and Western Europe such as Greece (127.2), Montenegro (123.8), and Belgium (123.5). Low rates were estimated for Finland (67.1), Switzerland (64.3), and Sweden (44.8). Among females, the highest incidence rates were seen in Ireland (85.1), Denmark (85.1), Hungary (76.6), Iceland (74.3) and the United Kingdom (71.4); the lowest rates were in Eastern Europe, notably Ukraine (11.8) and Belarus (10). Specifically, in the EU 5 countries, the ASRs of lung cancer for men were estimated to be 87.1/100,00 in Germany, 99.1/100,00 in Spain, 89.3/100,000 in the United Kingdom (UK), 90.9/100,000 in Italy and 103.9/100,000 in France. Similarly, the ASRs for women in these countries of interest were 52.4/100,000 in Germany, 29.9/100,000 in Spain, 71.4/100,000 in the UK, 35.1/100,000 in Italy and 44.2/100,000 in France (Figure 9 Dyba, 2021). Tobacco smoking is the largest preventable cause of lung cancer and contributes to greater than 80% to the occurrence of this disease. The trends in cigarette smoking shape the patterns of incidence rates observed in particular populations over the decades.

Among both women and men, the incidence of lung cancer is low in people aged <40 years and increases up to the age of 75–80 years in most populations.

Most newly diagnosed lung cancer patients have advanced disease: the proportion of stage IV and III disease at diagnosis differs from region to region but overall stage IV has been reported in 45.5% to 57.7% and stage III in 17% to 23% of patients (Walters, 2013). In a retrospective observational study (Minicozzi, 2018), stage at diagnosis (as TNM, condensed TNM, or Extent of Disease) was analysed for patients from 15 European countries grouped into 4 regions (Northern Europe, Central Europe, Southern Europe, and Eastern Europe), diagnosed with lung cancers between 2000 and 2007, 41% of patients had metastatic lung cancer at diagnosis. Eastern Europe had the lowest proportion of patients with metastatic disease (32% versus 41-48% in other regions) together with the highest proportion of patients with unknown stage disease (28% versus 9-18% in other regions).

Data from The European High-Resolution (HR) studies (http://hrstudies.it/) across 5 European countries (Belgium, Estonia, Portugal, Spain and Switzerland) from 2010- 2013, reported a 51.5% rate of TNM stage IV at diagnosis (ranging from 45.5% in Switzerland to 57.7% in Portugal).

An extrapolation based on European cancer registries from 12 countries reporting stage distribution of NSCLC at diagnosis estimated that 60 - 70% of patients were diagnosed at an advanced stage (Stages IIIB/C and IV) with 43 - 60% diagnosed at Stage IV. Other European studies, estimated the percentage of newly diagnosed NSCLC cancer, with stage IV ranges from 48% to 71% (Marchetti, 2011; Ilie, 2013; Brustugun, 2014; Horn, 2019; Debieuvre, 2022).

Thus, the overall rate of patients diagnosed with stage IIIB/C and IV lung cancers in European countries is estimated to be approximately 60%.

About 80–85% of lung cancer is non-small cell lung cancer, and 10–15% of lung cancer is small cell lung cancer and the rest is lung carcinoid tumor and other rare lung cancers (American Cancer Society, 2021). Non-small cell lung cancer is further sub-divided into 3 subtypes (Gridelli, 2015), 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%) (Travis, 2015). This is correlated by 2 European publications from Portugal and France (Guerreiro, 2020; Debieuvre, 2022).

NSCLC is comprised of an expanding number of biologically distinct and clinically relevant molecular subsets. Numerous molecular alterations have been recently reported and defined as driver oncogenes following their role in transforming and maintaining cancer cells in preclinical models. The most common targetable genetic alterations in lung cancer are EGFR- and KRAS activating mutations followed by, in frequency, ALK and ROS1 rearrangements, BRAF mutations, MET exon 14 skipping mutations and MET amplifications, RET gene fusions and HER2 mutations. NTRK and NRG1 gene fusions rarely occur in NSCLC (Kris, 2014; Jordan, 2017; Leonetti, 2018).

Approximately 2% to 4% of patients with NSCLC have mutations in the BRAF gene (Hendriks, 2023a) 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).

The vast majority of BRAF mutations occur in adenocarcinoma and very rarely in squamous cell carcinoma (Marchetti, 2011). In the German nation-wide CRISP registry that included 3,717 patients with advanced NSCLC, BRAF mutation was found in 4.4% of NSCLC (with 1.5% V600 and 2.6% non V600 mutation) and 0.3% of SC (Griesinger, 2021).

There is a probable slight female predilection for all BRAF mutations in NSCLC, with an average female-to-male ratio of 2 to 1 for the V600E mutation (Paik, 2011; Cardarella, 2013), with the exception of one Italian study that reported a dramatically higher female predilection for V600E mutations, with a female-to-male ratio of 8.6 to 1 (Marchetti, 2011). In a metanalysis (Cui, 2017) investigating the association between BRAF mutations and non-small cell lung cancer, 14 studies including 7,979 patients were analyzed for associations between the mutations of BRAF and gender. The results showed that 107 of 4,404 male patients (2.43%) were BRAF mutations positive and 108 (3.02%) of 3,575 female patients were BRAF mutations positive, indicating a significant difference of BRAF mutations between female and male (OR= 0.72, 95% CI=0.55–0.95, P=0.02). Forty-seven (32.6%) of 144 male patients were BRAFV600E mutations positive and 60 (62.5%) of 96 female patients were BRAFV600E mutations positive, indicating a significant difference in BRAFV600E mutations between female and male (OR=0.45, 95% CI=0.26–0.77, P=0.004).

The literature is divided as to an association with smoking status: whilst most studies conclude that BRAF mutations, in contrast to EGFR mutations, are commonly associated with a current or former status (54% to 100% of patients with BRAF mutations are current or former smokers (Yeh, 2013; 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).

BRAF mutations are less frequent in people of Chinese origin than in white individuals, occurring only in 0.5–2% of patients of Chinese origin affected by NSCLC (Li, 2014; Ding, 2017). A study performed on Japanese patients showed that the frequency of BRAF mutation was significantly higher in the Caucasian patients than in Asian ones (Izumi, 2020).

Histologically, BRAF V600E-mutated adenocarcinomas are mucinous with a micropapillary growth pattern and intense thyroid transcription factor-1 (TTF-1) expression (Alvarez, 2019) that is associated with shorter progression-free survival and overall survival in univariate analysis and multivariate analysis. BRAF non-V600E tumours were found to have micropapillary histology in only 12% of the cases.

Using the estimated value of 477,500 new lung cancer cases diagnosed in EU countries, and assuming that about 80% of newly diagnosed lung cancers are NSCLC, with 60% of stages IIIB/C or IV NSCLC and that approximately 3% of these cases are positive for BRAF mutations, with 50% of them driven by the BRAF V600E mutation (Class 1), it can be estimated that approximately 6,876 individuals presented with BRAF V600-mutated advanced lung cancer, of them 3,438 individuals with BRAF V600E mutation in 2020 across EU countries.

Demographics of the target population with unresectable, BRAF-mutated metastatic melanoma and risk factors for the disease:

The analysis from Globocan 2020 data identified a male to female ratio of ranging from 3 to 10 in Europe. The cumulative risk of lung cancer diagnosis before the age of 75 is also higher in males than females (5.4% for males corresponding to 1 in 19 men and 2.3% for females corresponding to 1 in 44 women (Dyba, 2021). However, a recent study (Debieuvre, 2022) showed increase in lung cancer in women and still a large proportion of patients diagnosed at metastatic or disseminated stage. In 2020, the proportion of women in patients diagnosed with lung cancer increased: 34·6% compared to 24·3% and 16·0% in 2010 and 2000 ($p<0·0001$). The proportion of non-smokers was higher in 2020 than in previous cohorts (12·6% compared to 10·9% in 2010 and 7·2% in 2000, $p<0·0001$). At diagnosis, 57·6% of patients had a metastatic/disseminated stage NSCLC. About 65.33% of men diagnosed with lung cancer are in the advanced local stage (stage III) or present metastases (stage IV) (Meza, 2015; Chen, 2014).

The myriad risk factors for lung cancer most commonly include lifestyle, environmental, and occupational exposures. The roles these factors play vary depending on geographic location, gender and race characteristics, genetic predisposition, as well as their synergistic interactions

- Cigarette smoking, and passive smoking

The World Health Organization (WHO) estimates that in 2012, lung cancer is the cause of 1.59 million deaths globally per year, with 71% of them caused by smoking. Tobacco smoking remains the main cause of lung cancer and the geographical and temporal patterns of the disease largely reflect tobacco consumption during the previous decades. In countries with active tobacco control measures, the incidence of lung cancer has begun to decline in men and in young and middle-aged women (Malvezzi, 2023). About 500 000 deaths annually are attributed to lung cancer in lifetime never-smokers (Toh, 2006). Absence of any history of tobacco smoking characterises 19% of female compared with 9% of male lung carcinoma in the United States (Novello, 2014; McCarthy, 2012). However, an increase in the proportion of NSCLC in never-smokers has been observed, especially in Asian countries (Couraud, 2015). These new epidemiological data have resulted in 'non-smoking-associated lung cancer' being considered a distinct disease entity, where specific molecular and genetic tumour characteristics have been identified (Couraud, 2015).

Both smoking prevention and smoking cessation can lead to a reduction in a large fraction of lung cancers.

The epidemiological evidence and biological plausibility support a causal association between second-hand exposure to cigarette smoke and lung cancer risk in nonsmokers (Samet, 2009; Jyoti, 2016) with the excess risk in the order of 20–30% for a nonsmoker being passive smoker (Hackshaw, 1997; Boffetta; 2002). The effect of involuntary smoking appears to be present for both household exposure, mainly from spousal and workplace exposure (Boffetta, 2002; Stayner, 2007),

and perhaps from involuntary childhood smoking exposure (Boffetta, 2000). Few studies have investigated the risk of lung cancer among users of smokeless tobacco products. In two large cohorts of US volunteers, the relative risk for spit tobacco use among nonsmokers was 1.08 (95% CI 0.64–1.83) and 2.00 (95% CI 1.23–3.24), respectively (Henley, 2005).

- Air pollution and other causes

Other factors such as genetic susceptibility, poor diet, occupational exposures and air pollution may act independently or in concert with tobacco smoking in shaping the descriptive epidemiology of lung cancer. Moreover, novel approaches in the classification of lung cancer based on molecular techniques have started to bring new insights to its aetiology, in particular among nonsmokers. (Malhotra, 2016; Corrales, 2020; Molina, 2008; Ole, 2013).

Natural history of advanced NSCLC in the population, including mortality and morbidity:

Natural History

The European Society for Medical Oncology (ESMO) estimates that approximately 50% of patients with NSCLC will develop metastases during the course of their disease (Hendriks, 2023a).

The mortality is associated with a high degree of malignancy and late diagnosis. As many as 65.33% of men diagnosed with lung cancer are in stage III or stage IV (Meza, 2015; Chen, 2014).

Mortality and Morbidity

In Europe, the age standardized rates of NSCLC mortality in 2020 have been estimated at 81.7/100,000 population in males and 29.0/100,000 population in females (Dyba, 2021). Non-Small Cell Lung Cancer is the leading cause of cancer deaths with more than 380 000 deaths corresponding to about 20% of the cancer deaths in Europe; this equals to an approximate 260,000 deaths in men and 120,000 deaths in women Europe-wide. Lung cancer represents the first cause of cancer mortality among males in all European countries apart from Sweden, and among females in 13 countries (one-third) of the European countries (Dyba, 2021).

Data from Eurocare 5 (Sant et al, 2023) found that the one-year age-standardized survival rate was 31% among stage III-IV patients, with survival being higher in females (39.3% (95% [IC: 26.7-30.3] survival) than males (25.4% survival 95% IC 35.8-42.8]). In addition, patients with any comorbidity at diagnosis had significantly higher relative excess of risk of death (RER) than those with no comorbidity (RER 1.09, CI, 1.01–1.18). The modelisation also showed that the adjusted RER of never smokers was lower than that of current smokers (RER 0.68, CI, 0.57–0.81).

More than half of people newly diagnosed with lung cancer can be expected to die within 1 year of diagnosis (Howlader, 2020).

Important co-morbidities:

With lung cancer being far more frequent in smokers and ex-smokers, these patients often have tobacco-related illnesses, mainly cardiovascular (ischaemic or hypertensive heart disease, lower limbs arteriopathy, etc.) and respiratory (chronic obstructive pulmonary disease (COPD), obstructive sleep apnoea, usual interstitial fibrosis… etc.) in nature. A Spanish real-world study assessed comorbidities at diagnosis in patients with lung cancer. In patients with non-squamous carcinoma (that includes predominantly adenocarcinoma) the following co-morbidities were most frequently reported: hypertension (42%), dyslipemia (28%), diabetes mellitus (19%), COPD (18%), cardiomyopathy (15%), depression/anxiety, former alcoholism and hypercholesterolemia (all 7%) (Provencio, 2022).

Cardiovascular diseases (CVDs) CVDs are one of the most common comorbidities in lung cancer with prevalence from 12,9% to 43% according to different studies (Islam, 2015).

A non-interventional cohort study (Linden, 2020) compared 3834 adult patients newly diagnosed with advanced NSCLC during 2006–2013 with the general population. The prevalence of analysed comorbidities was significantly higher for NSCLC patients compared to the general population, with an OR of 2.44 (95% CI 2.27–2.63). Respiratory diseases were the group of comorbidities that showed the largest difference between the cohorts with an OR of 7.22 (95% CI 6.46–8.07) where 22.7% of the patients in the regional NSCLC cohort and only 3.9% of the comparators were diagnosed. The group of comorbidities that showed the second largest OR between the two cohorts was infectious diseases with 2.50 (95% CI 2.25–2.77) followed by cardiovascular diseases with OR = 1.41 (95% CI 1.31–1.52).

The main existing treatment options for NSCLC with a BRAF-V600E mutation:

Historically, advanced NSCLC was primarily treated with platinum-based chemotherapy in first line. Advances in the understanding of tumour biology and the identification of oncogenic drivers, such as mutations in the EGFR gene and rearrangements of the ALK gene, have led to the development of targeted therapies such as tyrosine kinase inhibitors (TKIs). However, retrospective analysis exploring the activity of chemotherapy in participants with advanced NSCLC have revealed that advanced NSCLC participants harbouring a BRAF V600E mutation present a poor prognosis when treated with chemotherapy; 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 (Barlesi, 2016; Yan, 2022; O'Leary, 2019; Cardarella, 2013). While studies on the use of immune checkpoint inhibitors (ICIs) with a longer follow-up have confirmed that immunotherapy is the new standard of care for the first-line treatment of advanced or recurrent disease regardless of oncogene-addition status (Brahmer, 2022; De Castro, 2022; Johnson, 2022), there are very few 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 showed poor outcomes in BRAF-mutated participants (Mazieres, 2019).

Phase II trials have demonstrated the efficacy of BRAF and MEK inhibitors, for participants harbouring V600 mutation (with often no distinction between V600E and other V600 mutations). 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 (n = 101), ORR was 45%, mDoR 6.4 months, mPFS 5.2 months and mOS 10.0 months (Mazieres, 2019). In a Phase II study of dabrafenib in combination with trametinib in participants with BRAF V600E-mutated mNSCLC, the observed 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 in pretreated patients receiving the combination of dabrafenib and trametinib (Planchard, 2022). In treatment-naïve participants, with the combination of dabrafenib and trametinb, 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 pretreated and treatment-naïve participants, respectively, 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, 2022). The combination of dabrafenib-trametinib is approved by the EMA for the treatment of advanced NSCLC harbouring BRAF V600 mutations (Tafinlar EU SmPC-2023; Mekinist EU SmPC-2023).

The most recent ESMO and NCCN guidelines recommend dabrafenib and trametinib as first-line treatment for BRAF V600E mutated metastatic NSCLC in adults. Single agent vemurafenib or dabrafenib are treatment options if the preferred combination is not tolerated. If patients 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 (adenocarcinoma

or squamous cell carcinoma) (Hendriks, 2023a; Planchard, 2018; NCCN, 2023). In second line participants who have not received dabrafenib and trametinib, the ASCO guidelines (2022) consider giving dabrafenib and trametinib or dabrafenib or vemurafenib alone.

In a recent real-world study, a total of 53 patients with BRAF mutant NSCLC diagnosed between 2018 and 2022 were identified and included in the Glans-Look Lung Cancer Research database (Gibson, 2023): 35 V600E and 18 non-V600E; ICI-based systemic therapy was the most common systemic treatment chosen in the first-line setting in both V600E (44%) and non-V600E (70%) BRAF-mutant NSCLC. Among patients with a V600E mutation and advanced disease who received palliative systemic therapy, 49% received dual-targeted BRAF/MEK inhibition (dabrafenib and trametinib).

More recently (a real-life multicenter study (Perrone, 2022) conducted in consecutive NSCLC patients diagnosed between January 2018 and February 2020 identified 44 BRAF-mutant NSCLC patients: 23 V600E and 21 non-V600E. BRAF-V600E patients received first line chemotherapy (61%), targeted therapy (22%) or immunotherapy (17%). While patients treated with first-line targeted agents were excluded from the analysis, a worse performance of first-line immunotherapy versus first-line chemotherapy was observed in terms of OS in the BRAF V600E subpopulation as well as in the overall population.

The safety profile and toxicity management data of BRAFi and MEKi in NSCLC are mostly limited to the combination of dabrafenib and trametinib or translated from evidence obtained from melanoma. The toxicity profile of BRAF and MEK inhibitor combinations includes pyrexia, increases in blood levels of alanine aminotransferase, aspartate aminotransferase and creatine phosphokinase, nausea, vomiting and fatigue (Planchard, 2016; Planchard, 2017). Pyrexia (in the absence of infection) is related specifically to dabrafenib and is the most frequent adverse event (AE) reported with this treatment.

Part II: Module SII - Non-clinical Part of the Safety Specification

▪ Binimetinib single agent

Table SII.1: Key Safety Findings from Non-clinical Studies (toxicity, safety pharmacology)

Key Safety Findings	Relevance to human usage
TOXICITY	
• **Acute toxicity including important results from safety pharmacology studies** Binimetinib (also known as MEK162) did not have any adverse effects on cardiovascular (monkey telemetry), gastrointestinal motility and secretion (rats), neurobehavioral (Irwin rats), renal (rats) or respiratory function (rats) up to the highest single dose tested (100 mg/kg in rats and 10 mg/kg in monkeys). These doses are above the maximum tolerated doses (MTDs) determined in the multiple dose toxicity studies in rats and monkeys. In rats, no adverse effects on the main physiological functions were observed at 28fold the human exposure at the therapeutic dose level in terms of AUC_{0-24}. In monkeys, no cardiovascular effects were noted at similar human exposure at the therapeutic dose, based on mean area under the curve (AUC).	Not predictive for a safety concern.
• **Repeat-dose toxicity (by target organ for toxicity)** Repeated administration of binimetinib to rats is associated with abrasion, alopecia and scabbing of the skin, and minimal to mild increases in neutrophils and monocytes, alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea and phosphorus, and decreases in calcium and albumin. Test article related microscopic changes included cutaneous erosion/ulceration and multi-centric vascular and tissue mineralisation, which partially reversed after a treatment-free period. Skin lesions were dose-related in terms of severity and incidence and were partially reversible. Superficial gastric mucosal lesions and haemorrhagic ulcers were also seen in rats at doses that exceeded the MTD. The observations were observed with greater frequency and at lower dose level in females than in males. In cynomolgus monkeys, administration of binimetinib is associated with weight loss, soft stools, moderate decrease in red blood cell mass, increased platelet, monocyte and neutrophil counts, serum globulin, and decreases in serum albumin, and albumin:globulin ratio. All these changes were reversible after a treatment-free period. Treatment-related histologic findings included minimal to mild degeneration of the luminal epithelium	Potential concern of severe gastrointestinal bleeding due to gastric mucosal lesions. The frequency of severe gastrointestinal haemorrhage in the binimetinib arm was comparable to the comparator arm in the phase III CMEK162A2301 clinical study. The most frequently reported haemorrhage terms were epistaxis, retinal haemorrhage, haematoma and haematuria, with no particular predisposition to gastrointestinal haemorrhage. The following safety concerns are identified: • Hepatotoxicity • Skin toxicity

Key Safety Findings	Relevance to human usage
and mixed cell infiltrates in the large intestine, mucosal hyperplasia in the cecum, colon and/or rectum, which became more chronic and of reparative nature over time. All large intestinal findings resolved after a treatment-free period. Skin alterations were also observed in some animals, but they were sporadic and of low incidence. Minimal to mild mixed cell infiltrates in the parenchyma of the liver (considered secondary to the gastrointestinal toxicity) were observed at the end of the treatment period in the low and high-dose groups and were reduced at the end of the recovery period. There were also no treatment-related electrocardiographic abnormalities in monkeys and no ophthalmic changes in either rats or monkeys.	
• **Genotoxicity** There is no evidence of genotoxicity from two in vitro assays (bacterial reverse mutation test [Ames test] and mouse lymphoma assay [mouse L5178Y cells]) or from an in vivo assay (mouse erythrocyte micronucleus test).	Not predictive for a safety concern.
• **Carcinogenicity/mutagenicity** Binimetinib was negative for mutagenicity in both bacterial (Ames Assay; AB14DW.503.BTL) and mammalian (Mouse Lymphoma Assay; AB14DW.704.BTL) cell systems. Due to the nature of the target indication, in accordance with ICH S9, carcinogenicity studies have not been performed for binimetinib.	Not predictive for a safety concern.
• **Developmental and reproductive toxicity** Reproductive toxicity: Embryo-foetal development studies conducted in rats and rabbits showed evidence of embryo-toxicity (increased post-implantation loss and resorptions) and teratogenicity in rabbits (ventricular septal defects and pulmonary trunk alterations). In rats, only decreased ossification was observed and was considered to be secondary to decreased foetal body weight at maternally toxic doses. No teratogenic effects were noted in rats at 11-fold the human exposure at the therapeutic dose, based on AUC. Teratogenic effects, embryotoxicity and abortifacient effects were noted in rabbits at doses greater than those resulting in exposures assumed to be 2-fold the human exposure at the recommended clinical dose. No effect on reproductive organs was noted in either sex in the chronic, 6-month rat study, nor in any of the non-human primate toxicity studies.	Important potential risk of embryo-foetal toxicity.
Lactation: No studies are available. Excretion of the drug substance in milk was not evaluated.	Given the median age of the target population, the recommendation for effective contraception for women with potential of childbearing, and the

Key Safety Findings	Relevance to human usage
	severity of the disease, use during lactation is very limited.
Fertility: No studies were performed (in accordance with the requirements for oncology products). There was no toxicological observation in reproductive organs of rats and monkeys of either sex in repeat-dose toxicity studies.	Unknown relevance.
OTHER TOXICITY-RELATED INFORMATION OR DATA	
• **Phototoxicity/photosensitisation** Binimetinib showed very weak photosensitising potential in mice at exposures that were 3-fold above the mean systemic exposure attained in cancer patients at 45 mg BID. These data indicate that the clinical phototoxic risk of binimetinib is low in patients at therapeutic doses.	Not predictive for a safety concern. The potential concern of phototoxicity / photosensitisation was not supported by clinical data.
• **Drug interactions** <u>Effect of Cytochrome P 450(CYP) Enzymes on Binimetinib:</u> In vitro, CYP1A2 and CYP2C19 catalyse the formation of the active metabolite, AR00426032 (M3) by oxidative Ndemethylation.	The total relative contribution of oxidation to overall binimetinib metabolism is 2.4%, and is, therefore, unlikely to be clinically relevant. Not predictive for a safety concern.
<u>Effect of Binimetinib on CYP Substrates:</u> In vitro, binimetinib reversibly inhibits CYP2B6; however, in vivo inhibition of CYP2B6 is anticipated to be low based on calculated AUCR value of 1.03. Binimetinib is a weak reversible inhibitor of CYP1A2 and CYP2C9. Binimetinib is not considered a time-dependent inhibitor of CYP1A2, CYP2C9, CYP2D6 or CYP3A4/5. Binimetinib has also induced CYP3A in vitro.	In a drug-drug interaction study in healthy subjects, binimetinib did not alter the exposure of midazolam, indicating this induction is not clinically relevant. Not predictive for a safety concern.
<u>Effect of Transporters on Binimetinib:</u> In vitro experiments indicate that binimetinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Inhibition of P-gp or BCRP is unlikely to result in a clinically important increase in binimetinib concentrations as binimetinib exhibits moderate to high passive permeability. Binimetinib is not a substrate of organic anion transporting polypeptide (OATP1B1, OATP1B3, OATP2B1) or organic cation transporter 1 (OCT1) in vitro.	Potential risk but not important. No clinically relevant impact. Not predictive for a safety concern.
<u>Effect of Binimetinib on Transporters:</u> Binimetinib was found to be an inhibitor of OATP1B1 and OATP1B3. The estimated IC50 values for inhibition of OATP1B1 or OATP1B3-mediated uptake by binimetinib were 23.6±9.6 µM and ~29 µM, respectively. The highest reported mean C_{max}, total at 60 mg (0.629 µg/mL or 1.4 µM) divided by the IC50 values for OATP1B1 and OATP1B3 were <0.1 (0.06 and 0.05, respectively). The predicted increase in the AUC of	No clinically relevant impact. Not predictive for a safety concern.

Key Safety Findings	Relevance to human usage
sensitive OATP1B1 or OATP1B3 substrates was low (AUCR value of 1.01). Therefore, there is a low potential for binimetinib to cause a clinical drug interaction with substrates mainly cleared by OATPs at doses up to the MTD. Binimetinib was shown to be a weak inhibitor of OCT2 and did not inhibit the transport activity of OCT1 in vitro. As a result, binimetinib is unlikely to increase the systemic exposure to co-medications whose clearance is significantly mediated by OCT1 or OCT2 transport activity in vivo. Inhibition of OAT1 and OAT3 transporters by binimetinib was tested in vitro in study in study DMPK R1200819. The IC50 values for binimetinib inhibition of OAT1 and OAT3 activities in vitro were approximately 27 µM and 1.9 ± 0.17 µM, respectively. Models for determining whether this inhibition of OAT3 by binimetinib might cause a drug-drug interaction (DDI) and warrant a clinic DDI study was applied and no clinically significant interaction is expected based on the results.	
<u>Effect of UGT1A1 Inducers or Inhibitors on binimetinib:</u> Binimetinib is primarily metabolized through UGT1A1 mediated glucuronidation. In clinical study sub-analysis, however, there was no apparent relationship observed between binimetinib exposure and UGT1A1 mutation status. In addition, simulations to investigate the effect of 400 mg atazanavir (UGT1A1 inhibitor) on the exposure of 45 mg binimetinib predicted similar binimetinib C_{max} in the presence or absence of atazanavir. No formal clinical study conducted with UGT1A1 inhibitors or inducers.	The possible extent of drug interactions mediated by UGT1A1 is minimal, and unlikely clinically relevant. Not predictive for a safety concern.
Safety pharmacology studies were conducted in rats and monkeys to assess the effects of binimetinib on key organ systems (cardiovascular, respiratory, neurobehavioral, renal and GI function). There were no significant in vivo safety findings at doses up to 100 mg/kg in rats and 10 mg/kg in monkeys. Binimetinib and its active metabolite, AR00426032, showed no significant human ether-a-go-go-related gene (hERG) channel inhibition (IC_{50} value of each > 30µM), indicating a low clinical risk of inducing QT interval corrected for heart rate (QTc) prolongation.	Not predictive for a safety concern.
Two non-Good Laboratory Practice (GLP) exploratory safety pharmacology studies demonstrated that binimetinib had no effect on normal wound healing in the mouse and had a potential beneficial effect (survival protection) on immune modulation in the mouse. In addition, secondary pharmacodynamic evaluations showed that binimetinib demonstrated high selectivity for MEK versus over 200 other kinases. Therefore, off-	These data support the use of binimetinib in surgical settings or in immune-challenged patients, as this compound is unlikely to produce deleterious effects in post-surgical clinical settings (e.g., tumor resection) or hospitalized patients.

Key Safety Findings	Relevance to human usage
target kinase activity at relevant free-therapeutic concentrations in vivo is not anticipated. **Preclinical cardiovascular safety pharmacology** data for both binimetinib and encorafenib do not indicate a clinical risk for QT interval corrected for heart rate (QTc) prolongation based on the findings of the hERG assay and ECG evaluation in the GLP 4-week monkey study. There were no clinical signs in the encorafenib 4-week GLP rat and monkey studies or in the binimetinib safety pharmacology studies that would indicate an effect on the CNS or respiratory system. Based on the safety pharmacology data, the combination of binimetinib + encorafenib is not expected to have adverse effects on the cardiovascular, CNS or respiratory systems.	

▪ Binimetinib in combination use

Binimetinib in combination with encorafenib

When combining two compounds, the potential for overlapping toxicities based on the non-clinical data needs to be considered. No binimetinib and encorafenib combination toxicity studies have been conducted. A summary of an integrative assessment of the potential for additive and/or synergistic toxicity of combining binimetinib with encorafenib is described below for safety pharmacological data, and an exhaustive summary of potential integrative toxicity is tabulated by target organ. Some of the effects reported in this table were mainly observed in moribund or dead females at very high dose levels, and as such were not reported as relevant single agent findings.

Potential synergistic toxicity from safety pharmacology data

Non-clinical cardiovascular safety pharmacology data for both binimetinib and encorafenib as single agents do not indicate a clinical risk for QT prolongation based on the findings of the hERG assay and in vivo ECG evaluation in the GLP telemetry and repeat-dose toxicity studies in monkeys. There were no clinical signs in the binimetinib or the encorafenib safety pharmacology studies and GLP repeat-dose studies in rats and monkeys that indicate an effect on the CNS or respiratory system. Based on the preclinical data, the combination of binimetinib and encorafenib is not expected to have adverse effects on the cardiovascular, CNS or respiratory systems.

Potential synergistic toxicity from toxicological assessment by organ

According to the resulting potential for synergistic toxicity, it appears likely that gastrointestinal intolerance/toxicity, skin toxicity and myelosuppression could be dose limiting in the clinical setting when binimetinib and encorafenib are combined.

Table SII.2: Binimetinib and encorafenib combination: Integrative toxicological assessment of the binimetinib and encorafenib combination from single agent non-clinical safety findings

Target Organ	Binimetinib	Encorafenib	Potential impact of combination
Adrenal	Tissue mineralization (rat)	Cortical cytoplasmic vacuolation (rat)	None predicted
Aorta	Tissue mineralization (rat)	No change	None predicted

Target Organ	**Binimetinib**	**Encorafenib**	**Potential impact of combination**
Bone	Marrow necrosis, osteopenia, thickening of the physis (rat)	Marrow hypocellularity (rat)	Potential for synergistic toxicity
Epididymes	No change	Oligospermia (rat)	None predicted
Gastrointestinal tract	Tissue mineralization (rat), degeneration of the absorptive mucosal epithelium and mucosal mixed cell inflammation in the cecum, colon and/or rectum (monkey)	Non-glandular stomach in rat, hyperkaratosis and epithelial hyperplasia, Stomach erosions (rat)	Potential for synergistic toxicity
Heart	Tissue mineralization (rat)	No change	None predicted
Kidney	Tissue mineralization (rat)	Vacuolation of tubular epithelium (rat)	None predicted
Liver	No change	Hepatocellular cytoplasmic vacuolation	None predicted
Lung	Tissue mineralization (rat)	No change	None predicted
Ovaries	Tissue mineralization (rat)	No change	None predicted
Pancreas	No change	Decreased zymogen, cytoplasmic vacuolation	None predicted
Pituitary	Tissue mineralization (rat)	No change	None predicted
Prostate	Tissue mineralization (rat)	No change	None predicted
Retina	No change	Blistering (CSR-like)(monkey), retinal detachment	None predicted[a]
Skin	Hair loss/scabbing, erosion, inflammation and ulceration (rat)	Scaly and/or thickened area of skin on plantar surfaces of rear feet: histopathology focal to multifocal areas of slight to marked hyperkeratosis,	Potential for synergistic toxicity[b]

Target Organ	Binimetinib	Encorafenib	Potential impact of combination
		squamous cell hyperplasia and inflammatory cell infiltration (rat)	
	Low phototoxic potential	Phototoxic potential	
Spleen	No change	Lymphoid depletion/atrophy (rats)	None predicted
Testis	No change	Tubular degeneration and cytoplasmic vacuolation of seminiferous tubules (rat)	None predicted
Thymus	No change	Lymphoid depletion	None predicted
Tongue	Tissue mineralization (rat)	No change	None predicted

[a] Human clinical experience reveals retinal findings with binimetinib as a single agent.
[b] Human clinical experience reveals less skin toxicity when binimetinib and binimetinib are dosed in combination.

Conclusions

The non**-**clinical safety findings of **binimetinib** that are considered relevant and potentially important for humans, and that are thus carried forward for discussion to Sections SVII and SVIII as risks (either important or not important) are:

- Severe dermatologic reactions
- Hepatotoxicity
- Embryo-foetal toxicity

The non-clinical safety findings from **binimetinib and encorafenib** compounds that are considered relevant and potentially important for humans for causing additive or synergistic toxicity when administered in combination, and that are carried forward for discussion to SVII and SVIII as risks are:

- Bone toxicity leading to myelosuppression
- Gastrointestinal toxicity
- Dermatologic reactions.

Part II: Module SIII - Clinical Trial Exposure

▪ Binimetinib single agent

Safety data from 4 clinical studies using binimetinib as a single agent are taken into account in the exposure data presented in this single agent part of the RMP. The following 4 clinical studies have been pooled in the Broad Safety Set:

- CMEK162A2301 [Phase III]
- CMEK162X2201 [Phase II]
- CMEK162X1101 [Phase I]
- ARRAY-162-111 [Phase I]

In addition to the safety data from the clinical studies mentioned above, data from ongoing named-patient programmes, compassionate use protocols and investigator-sponsored trials with single-agent binimetinib in the relevant NRAS/BRAF-mutant metastatic melanoma population have been collected (studies CMEK162AUS08T, CMEK162XCH02T, CMEK162A2001I and ARRAY-NPP-162-401). The safety data obtained are limited but consistent with the clinical trial data of the Broad Safety Set.

The analysed populations were:

- The broad safety set (N=566), includes pooled data from 4 clinical studies in patients with advanced solid tumours treated with single agent binimetinib at doses from 30 mg BID to 80 mg BID, including patients with melanoma (*NRAS* mutation Q61positive and *BRAF* mutationpositive) (Table SIII.1).
- The binimetinib safety set (N=427), the 'Bini 45 P population', includes pooled data from 2 clinical studies (CMEK162A2301 [Phase III] and CMEK162X2201 [Phase II]), in which patients with metastatic melanoma (including *NRAS* mutation-positive and *BRAF*-mutation positive) were treated with single agent binimetinib at the recommended dose of 45 mg BID (Table SIII.1). This population is the basis for the calculation of adverse drug reaction (ADR) frequencies.

Table SIII.1: Analysed Populations

Database	**Studies**	**Pooled Treatment Groups**
Bini 45 P Safety Set N=427	CMEK162A2301 (Phase III) CMEK162X2201 (Phase II)	binimetinib 45 mg BID, 269 patients 45 mg BID, 158 patients
Broad Safety Set N=566	CMEK162A2301 (Phase III) CMEK162X2201 (Phase II) CMEK162X1101 (Phase I) ARRAY-162-111 (Phase I)	binimetinib 45 mg BID, 269 patients 45 mg BID, 158 patients 60 mg BID, 25 patients 30 mg BID, 6 patients 45 mg BID, 15 patients 30 mg BID, 4 patients 45 mg BID, 44 patients 60 mg BID, 41 patients 80 mg BID, 4 patients

Data are presented with the data cut-off of 18 March 2016 for the Study CMEK162A2301, 06 November 2015 for Study CMEK162X2201; 10 February 2014 for Study CMEK162X1101 and 23 January 2013 for the completed Study ARRAY-162-111.

The data cut-off for the analysis of the broad safety set (N=566) and the Bini 45 P was 18 March 2016.

A summary of overall exposure and duration of exposure is provided below overall, by dose, age group and gender, and by ethnic or racial origin. Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375 i.e. the mean number of days per month. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.

1. Duration of exposure

Table SIII.2: Exposure, by Duration and Treatment Group (Broad Safety Set and Bini 45 P)

Exposure Variable	**All Cancers Binimetinib Any Dose (N=566)**	**All Melanoma Bini 45 P (N=427)**
Duration of Exposure (Weeks)		
Mean (SD)	18.0 (21.11)	18.9 (19.47)
Median	12.0	13.0
Min to Max	0 to 190	0 to 183
Duration of Exposure Category (Weeks) – n (%)		
<3	42 (7.4)	22 (5.2)
≥3 to <6	68 (12.0)	43 (10.1)
≥6 to <9	111 (19.6)	70 (16.4)
≥9 to <12	57 (10.1)	50 (11.7)
≥12 to <18	114 (20.1)	98 (23.0)
≥18 to <24	45 (8.0)	38 (8.9)
≥24 to <30	39 (6.9)	31 (7.3)
≥30 to <36	26 (4.6)	24 (5.6)
≥36 to <42	16 (2.8)	14 (3.3)
≥42 to <48	9 (1.6)	7 (1.6)
≥48 to <54	9 (1.6)	7 (1.6)
≥54 to <60	7 (1.2)	6 (1.4)
≥60 to <66	7 (1.2)	6 (1.4)
≥66 to <72	3 (0.5)	3 (0.7)
≥72 to <78	1 (0.2)	0
≥78	12 (2.1)	8 (1.9)
Patient-months	**2346.6**	**1857.4**

Sources: Table M5.3.5.3 RMP1-1.

2. By age group and gender

Table SIII.3: Exposure by Age Category and Gender (Broad Safety Set and Bini 45 P)

Age/Gender Category	**All Cancers Binimetinib Any Dose (N=566)**		**All Melanoma Bini 45 P (N=427)**	
	Patients	**Patient-months**	**Patients**	**Patient-months**
Gender Category				
Male	350	1463.1	272	1194.7
Female	216	883.5	155	662.7
Age Category				
<65 years	332	1426.5	227	1013.8
≥65 years	234	920.1	200	843.5
Age and Gender Category				
Male <65 years	199	850.4	143	629.2
Male ≥65 years	151	612.6	129	565.5
Female <65 years	133	576.1	84	384.6
Female ≥65 years	83	307.4	71	278.0

Sources: Tables M5.3.5.3 RMP1-2, M5.3.5.3 RMP1-3, and M5.3.5.3 RMP1-4.

3. By ethnic or racial origin

Table SIII.4: Exposure by Ethnic and Racial Origin (Broad Safety Set and Bini 45 P)

	All Cancers Binimetinib Any Dose (N=566)		**All Melanoma Bini 45 P (N=427)**	
	Patients	**Patient-months**	**Patients**	**Patient-months**
Ethnicity Category				
Caucasian	504	2101.7	399	1758.9
Asian	31	129.2	7	21.3
Other	31	115.7	21	77.2
Race Category				
Hispanic or Latino	22	85.5	14	77.1
Non Hispanic or Non Latino	542	2257.4	413	1780.3
Missing	2	3.7	0	0

Sources: Tables M5.3.5.3 RMP1-5 and M5.3.5.3 RMP1-6.

- **<u>Binimetinib in combination with encorafenib</u>**

Safety data from 5 supportive clinical trials using binimetinib in combination with encorafenib in patients with unresectable or metastatic melanoma are included in this RMP for the combination of binimetinib and encorafenib for the treatment of patients with unresectable or metastatic *BRAF* V600-mutant melanoma. Of them, 3 clinical trials which summarise the safety of the combination of binimetinib and encorafenib are presented below for this RMP.

CMEK162B2301 is the phase III pivotal study for the melanoma indication in the target population. Patients were randomised and treated in 3 arms: encorafenib 300 mg QD arm (N=192), combination encorafenib 450 mg QD and binimetinib 45 mg BID (N=192) and vemurafenib comparator arm at the recommended dose (N=186).

CLGX818X2109 is a Phase II, multi-center, open-label study of sequential LGX818/MEK162 combination followed by a rational combination with targeted agents after progression, to overcome resistance in adult participants with locally advanced or metastatic BRAF V600 melanoma. In Part 1 of this study, patients were treated with combination of encorafenib 450 mg QD and binimetinib 45 mg BID, a total of 158 patients were enrolled in part 1, of whom 75 were BRAF/MEK-treatment naïve.

CMEK162X2110 is a Phase Ib/II, multi-center, open-label, dose escalation study of LGX818 in combination with MEK162 in adult participants with BRAF V600 - dependent advanced solid tumours. Among the total included patients, 7 of the patients with melanoma were BRAF/MEK naive and treated with combination encorafenib 450 mg QD and binimetinib 45 mg BID.

In the safety data analyses for melanoma:

- 'Combo 450' refers to the combination of encorafenib 450 mg QD and binimetinib 45 mg BID patients in Study CMEK162B2301 (N=192). When appropriate, to avoid confusion with other populations, this population is referred to as Combo 450 arm of study CMEK162B2301.
- 'Combo 450 RP' refers to the restricted combination safety pool for patients who received doses of encorafenib at 450 mg QD in combination with binimetinib at 45 mg BID (N=274). This population is named Combo 450 RP in the first MAA of binimetinib 45 mg BID and encorafenib 450 mg QD for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. This population is named the "Melanoma population" in the dossier supporting the MAA of binimetinib 45 mg BID and encorafenib 450 mg QD for the treatment of adult patients with advanced non-small cell lung cancer with a BRAFV600E mutation. In this RMP, the 2 names may be used depending on the context ("**Melanoma population"** or "**Combo 450 RP**").
- 'Combo BP for melanoma' refers to the broad combination safety pool for patients who received doses of encorafenib ranging from 400 mg to 600 mg QD in combination with binimetinib at 45 mg BID (N=433); Note that 4 patients were included in both CMEK162X2110 and CLGX818X2109.

The binimetinib and encorafenib combination "broad" safety population for melanoma includes data from 433 patients with metastatic melanoma, who were previously naïve to BRAF inhibitors, enrolled at or randomised to a dose of encorafenib ranging from 400 mg to 600 mg QD in combination with binimetinib at 45 mg BID as summarised in the following table:

Table SIII.5a: Binimetinib and encorafenib combination: Clinical studies relevant to safety evaluation- Combo BP for melanoma (N=433)

Binimetinib and encorafenib combination (melanoma)		
	Cut-off date	**Patients included in the integrated summary of safety**
CMEK162B2301	09 Nov 2016	192
CLGX818X2109	30 Dec 2016	158*
CMEK162X2110	31 Dec 2016	87*

*Sources: 2.7.4 Summary of clinical safety - LGX818/MEK162** 4 patients were included in both CMEK162X2110 and CLGX818X2109

Table SIII.5b: Clinical studies Supportive for Binimetinib/Encorafenib therapy in Combo 450 RP (N=274) - Melanoma indication

Binimetinib and encorafenib combination (melanoma)		
	Cut-off date	**Patients included in the integrated summary of safety**
CMEK162B2301	09 Nov 2016	192
CLGX818X2109	30 Dec 2016	75
CMEK162X2110	31 Dec 2016	7
Total		**274**

Source: 2.7.4 Summary of clinical safety (NSCLC)

For advanced non-small cell lung cancer (NSCLC) with a BRAF V600E mutation, safety data from a supportive pivotal study (PHAROS study; C4221008; ARRAY 818-202) using binimetinib (45 mg BID) in combination with encorafenib (450 mg QD) are included in this RMP. The PHAROS study is an ongoing open-label, multicentre, non-comparative, Phase 2 study to determine the safety, tolerability and antitumour activity of the combination of encorafenib and binimetinib in participants with BRAF V600-mutant NSCLC. A total of 98 patients were enrolled in this study and received at least 1 dose of study treatment.

Safety data from the PHAROS study were integrated with data from studies in other indication using the same dosage and administration schedule of the combination of binimetinib and encorafenib. This integrated data approach is in accordance with the regulatory guidance and the currently approved labelling of binimetinib. Accordingly, 4 studies included in the analyses for binimetinib 45 mg BID in combination with Encorafenib 450 mg QD and are described below.

Integrated safety data are presented for 372 patients, hereafter referred to as the **Combo 450 ISP** (Integrated safety population):

- 98 patients with BRAF V600E mutant advanced NSCLC enrolled at a dose of 45 mg BID binimetinib plus 450 mg QD encorafenib from the PHAROS study referred to as the **NSCLC population** at a data cut-off of 22 January 2023.

- 274 patients with BRAF V600 mutant metastatic melanoma enrolled at or randomised to a dose of 45 mg BID binimetinib plus 450 mg QD encorafenib (192 patients from Study CMEK162B2301, 75 patients from Study CLGX818X2109 and 7 patients from Study CMEK162X2110) referred to as the Melanoma population (Combo 450 RP) and corresponding to the previously submitted safety data for the melanoma indication in the first MAA of the combination of binimetinib plus encorafenib.

As such, **Combo broad ISP population** (N= 531) includes the 'Combo BP for melanoma' (N=433) plus the 'NSCLC population' (N=98).

Table SIII.5c: Binimetinib and encorafenib combination: Supportive clinical studies for Combo 450 ISP:

Encorafenib and binimetinib combination (Combo 450 ISP)		
	Cut-off date	**Patients included in the 45 Combo ISP**
CMEK162B2301	09 Nov 2016	192
CLGX818X2109	30 Dec 2016	75
CMEK162X2110	31 Dec 2016	7
ARRAY 818-202 (C4221008)	22 Jan 2023	98
Total	**372**	

Source: 2.7.4 Summary of Clinical Safety – NSCLC

A summary of overall exposure and duration of exposure is provided below for the restricted (i.e; by indication) and the integrated combination population, by dose, age group and gender, and by ethnic or racial origin (person time = patient months).

1. Duration of exposure

Table SIII.6a: Binimetinib and Encorafenib combination: Duration of exposure (Combo 450 ISP)

Combination integrated safety population (Combo 450 ISP; N=372)		
Duration of exposure (at least)	**Persons**	**Patient-months**
1 month	353	5125.7
3 months	327	5076.3
6 months	273	4822.0
12 months	176	3967.7
18 months	130	3286.3
24 months	63	1856.9
30 months	21	726.8
Total	**372**	**5135.3**

Sources: W00090_NSCLC - Version date: 31MAY2023 13:48 - File Name: Sub5_1_1_c1_RMPexp_treat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 – PGM Sub5_1_1_c1_RMPexp_treat_t.sas 04MAY2023 11:17
Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient.
Duration of exposure is defined as the max exposure between Encorafenib and binimetinib.
Duration of Exposure = (date of last exposure to study drug - date of first exposure to study drug +1)/30.4375

Melanoma indication (Combo 450 RP; N=274)		
Duration of exposure (at least)	**Persons**	**Patient-months**
1 month	265	3827.02
3 months	255	3806.09
6 months	213	3606.67
12 months	133	2901.06
18 months	97	2362.84
24 months	41	1163.34
30 months	9	301.73
Total	**274**	**3831.75**

Sources: ISS_Part1_u: table 1.5.1.1.1c
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.

NSCLC indication (N=98)		
Duration of exposure (at least)	**Patients**	**Patients-Months**
1 month	88	1298.6
3 months	72	1270.2
6 months	60	1215.4
12 months	43	1066.6
18 months	33	923.4
24 months	22	693.6
30 months	12	425.1
Total	**98**	**1303.5**

Sources: W00090_NSCLC - Version date: 31MAY2023 13:52 - File Name: Sub5_2_1_c1_RMPexp_PHtreat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_1_c1_RMPexp_PHtreat_t.sas 04MAY2023 11:16
Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient.
Duration of exposure is defined as the max exposure between Encorafenib and binimetinib.
Duration of Exposure = (date of last exposure to study drug - date of first exposure to study drug +1)/30.4375

Table SIII.6b: Binimetinib and encorafenib combination: Duration of exposure (Combo broad population)

Broad combination integrated safety population (Combo broad ISP; N=531)		
Duration of exposure (at least)	**Persons**	**Patient-months**
1 month	500	6494.3
3 months	433	6367.9
6 months	343	5957.9
12 months	214	4827.7
18 months	150	3880.8
24 months	76	2314.4
30 months	31	1110.9
Total	**531**	**6512.2**

Sources: ISS_Part1_u: table 1.5.1.1.1d
Sources: W00090_NSCLC - Version date: 31MAY2023 13:52 - File Name: Sub5_2_1_c1_RMPexp_PHtreat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_1_c1_RMPexp_PHtreat_t.sas 04MAY2023 11:16
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.

2. By dose

Table SIII.7a: Binimetinib and encorafenib combination: Dose of exposure (Combo 450 ISP)

Combination integrated safety population (Combo 450 ISP; N=372)		
Dose of exposure (at least)	**Persons**	**Patient-months**
Encorafenib 450mg QD + Binimetinib 45 BID	372	5135.3
Total	**372**	**5135.3**

Sources: W00090_NSCLC - Version date: 31MAY2023 13:48 - File Name: Sub5_1_2_c1_RMPexpDos_treat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_1_2_c1_RMPexpDos_treat_t.sas 04MAY2023 11:17
Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient.
Duration of exposure is defined as the max exposure between Encorafenib and binimetinib.
Duration of Exposure = (date of last exposure to study drug - date of first exposure to study drug +1)/30.4375

Melanoma indication (Combo 450 RP; N=274)		
Dose of exposure	**Persons**	**Patient-months**
Binimetinib 45 BID + Encorafenib 450mg QD	274	3831.75
Total	**274**	**3831.75**

Sources: ISS_Part1_u: table 1.5.1.1.2c
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment – date of first administration of study treatment +1.

NSCLC indication (N=98)		
Dose of exposure (at least)	**Persons**	**Patient-months**
Encorafenib 450mg QD + Binimetinib 45 BID	98	1303.5
Total	**98**	**1303.5**

Sources: W00090_NSCLC - Version date: 31MAY2023 13:52 - File Name: Sub5_2_2_c1_RMPexpDos_PHtreat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_2_c1_RMPexpDos_PHtreat_t.sas 04MAY2023 11:16
Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient.
Duration of exposure is defined as the max exposure between Encorafenib and binimetinib.
Duration of Exposure = (date of last exposure to study drug - date of first exposure to study drug +1)/30.4375

Table SIII.7b: Binimetinib and encorafenib combination: Dose of exposure (Combo broad population)

Broad combination integrated safety population (Combo broad ISP; N=531)		
Dose of exposure	**Persons**	**Patient-months**
Encorafenib 400mg QD + Binimetinib 45 BID	4	21.49
Encorafenib 450mg QD + Binimetinib 45 BID	465	5805.4
Encorafenib 600mg QD + Binimetinib 45 BID	62	685.27
Total	**531**	**6512.2**

Sources: ISS_Part1_u: table 1.5.1.1.2d
Sources: W00090_NSCLC - Version date: 31MAY2023 13:52 - File Name: Sub5_2_2_c1_RMPexpDos_PHtreat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_2_c1_RMPexpDos_PHtreat_t.sas 04MAY2023 11:16
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.

3. By age group and gender

Table SIII.8a: Binimetinib and encorafenib combination: Exposure by age group and gender (Combo 450 ISP)

Combination integrated safety population (Combo 450 ISP; N=372)				
	Persons		**Patient months**	
Age group [1]	**M**	**F**	**M**	**F**
18 - 64 years	135	95	1921.3	1402.2
65 - 74 years	61	46	830.2	598.0
75 - 84 years	17	15	162.5	212.8
85+ years	2	1	5.0	3.2
Total	**215**	**157**	**2919.1**	**2216.2**

Sources: W00090_NSCLC - Version date: 31MAY2023 13:49 - File Name: Sub5_1_3_c1_RMPexpAgSex_treat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_1_3_c1_RMPexpAgSex_treat_t.sas 04MAY2023 11:17
Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient. Duration of exposure is defined as the max exposure between Encorafenib and binimetinib.
Duration of Exposure = (date of last exposure to study drug - date of first exposure to study drug +1)/30.4375
[1] Patients under 18 years was an exclusion criterion

Melanoma indication (Combo 450 RP; N=274)				
	Persons		**Patient months**	
Age group [1]	**M**	**F**	**M**	**F**
18 - 64 years	116	78	1690.58	1077.78
65 - 74 years	45	20	556.55	336.20
75 - 84 years	8	6	79.87	87.56
85+ years	.	1	.	3.22
Total	**169**	**105**	**2327.00**	**1504.76**

Sources: ISS_Part1_u: table 1.5.1.1.3c
[1] Patients under 18 years was an exclusion criterion.
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.

NSCLC indication (N=98)				
	Persons		**Patient-months**	
Age group [1]	**M**	**F**	**M**	**F**
18 - 64 years	19	17	230.8	324.4
65 - 74 years	16	26	273.7	261.8
75 - 84 years	9	9	82.6	125.2
85+ years	2	-	5.0	-
Total	**46**	**52**	**592.1***	**711.5***

Sources: W00090_NSCLC - Version date: 31MAY2023 13:53 - File Name: Sub5_2_3_c1_RMPexpAgSx_PHtreat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_3_c1_RMPexpAgSx_PHtreat_t.sas 04MAY2023 11:16
Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient. Duration of exposure is defined as the max exposure between Encorafenib and binimetinib.
Duration of Exposure = (date of last exposure to study drug - date of first exposure to study drug +1)/30.4375
[1] Patients under 18 years was an exclusion criterion
** Cumulative numbers may not exactly match the sum of numbers listed in the table due to rounding*

Table SIII.8b: Binimetinib and encorafenib combination: Exposure by age group and gender (Combo broad population)

Broad combination integrated safety population (Combo broad ISP; N=531)				
	Persons		**Patient-months**	
Age group [1]	**M**	**F**	**M**	**F**
18 - 64 years	204	150	2575.7	1868.6
65 - 74 years	79	53	946.0	643.4
75 - 84 years	22	18	186.6	241.9
85+ years	2	3	5.0	44.78
Total	**307**	**224**	**3713.4**	**2798.8**

Sources: ISS_Part1_u: Table 1.5.1.1.3d
Sources: W00090_NSCLC - Version date: 31MAY2023 13:53 - File Name: Sub5_2_3_c1_RMPexpAgSx_PHtreat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_3_c1_RMPexpAgSx_PHtreat_t.sas 04MAY2023 11:16
[1] Patients under 18 years was an exclusion criterion.
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.

4. By ethnic or racial origin

Table SIII.9a: Combination: Exposure by ethnic or racial origin (Combo 450 ISP)

Combination integrated safety population (Combo 450 ISP; N=372)		
Racial origin [1]	**Persons**	**Patient-months**
Asian	13	165.5
Black or African American	3	4.9
Caucasian	347	4864.8
Other	5	79.1
Unknown[2]	4	21.0
Total	**372**	**5135.3**

Sources: W00090_NSCLC - Version date: 31MAY2023 13:49 - File Name: Sub5_1_4_c1_RMPexpRace_treat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_1_4_c1_RMPexpRace_treat_t.sas 04MAY2023 11:17
Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient. Duration of exposure is defined as the max exposure between Encorafenib and binimetinib.
Note: No black patients were included in the pool of melanoma indication (source ISS table 1.2)
Duration of Exposure = (date of last exposure to study drug - date of first exposure to study drug +1)/30.4375
[1] In this table, the 'other' group does not include 'Black' origin
[2] Patients with missing value or with value equal to 'Not reported due to confidentiality reason' were included in the unknown category

Melanoma indication (Combo 450 RP; N=274)

Racial origin [1]	Persons	Patient-months
Asian	6	72.54
Caucasian	261	3685.16
Other	4	57.79
Unknown*	3	16.26
Total	**274**	**3831.75**

Sources: ISS_Part1_u: table 1.2, table 1.5.1.1.4c
[1] No blacks were included in the pool of melanoma indication
*Patients with missing value were included in the unknown category
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.

NSCLC indication (N=98)

Racial origin [1]	Persons	Patient-months
Asian	7	93.0
Black or African American	3	4.9
Caucasian	86	1179.7
Other	1	21.3
Unknown[2]	1	4.7
Total	**98**	**1303.5***

Sources: W00090_NSCLC - Version date: 31MAY2023 13:53 - File Name: Sub5_2_4_c1_RMPexpRace_PHtreat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_4_c1_RMPExpRace_PHtreat_t.sas 04MAY2023 11:20
Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient. Duration of exposure is defined as the max exposure between Encorafenib and binimetinib.
Duration of Exposure = (date of last exposure to study drug - date of first exposure to study drug +1)/30.4375
[1] In this table, the 'other' group does not include 'Black' origin
[2] Patients with missing value or with value equal to 'Not reported due to confidentiality reason' were included in the unknown category
** Cumulative numbers may not exactly match the sum of listed numbers due to rounding*

Table SIII.9b: Combination: Exposure by ethnic or racial origin (Combo broad population)

Broad combination integrated safety population (Combo broad ISP; N=531)

Racial origin [1]	Persons	Patient-months
Asian	15	185.0
Caucasian	499	6154.7
Black or African American	3	4.9
Other	10	146.6
Unknown[2]	4	20.9
Total	**531**	**6512.2**

Sources: ISS_Part1_u: table 1.2, table 1.5.1.1.4d
Sources: W00090_NSCLC - Version date: 31MAY2023 13:53 - File Name: Sub5_2_4_c1_RMPexpRace_PHtreat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_4_c1_RMPExpRace_PHtreat_t.sas 04MAY2023 11:20
[1] No blacks were included in the pool of melanoma indication (source table 1.2)
[2] Patients with missing value or with value equal to 'Not reported due to confidentiality reason' were included in the unknown category
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.

Part II: Module SIV - Populations not studied in clinical trials involving binimetinib

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

- **Binimetinib single agent**

The most relevant exclusion criteria in pivotal clinical studies within development programme specific to binimetinib single agent are the following:

Uncontrolled arterial hypertension despite appropriate medical therapy

Reason for exclusion: There is potential for worsening of pre-existing severe and uncontrolled hypertension, with end-organ complications that are potentially serious or life-threatening.

Is it considered to be included as missing information? No

Rationale: Hypertension was included as an important identified risk for binimetinib and was addressed in the relevant section of the binimetinib RMP. This risk was removed from the list of safety concerns of binimetinib in the last approved version of binimetinib RMP (Version 2.0; dated on 24 Apr 2020) in line with the approach of the revised GVP Module V (Rev 2), as hypertension is considered as clinically manageable and recommendations for monitoring and management of hypertension are mentioned in the binimetinib SmPC, and considered as routine pharmacovigilance activities. Furthermore, the impact to the individual is expected to be very low considering the seriousness of the advanced cancer.

Patients who are planning on embarking on a new strenuous exercise regimen and patients with neuromuscular disorders associated with elevated CK

Reason for exclusion: Due to the potential impact on evaluation of MEK-induced muscular toxicity e.g. important CK elevation and the potentially serious and life-threatening rhabdomyolysis, patients undertaking strenuous exercise regimens or with known neuromuscular disorders, associated with CK elevation were excluded to minimise confounding factors. There is no information on the potential effects of binimetinib in patients with neuromuscular disorders.

Is it considered to be included as missing information? No

Rationale: Rhabdomyolysis was included as an important identified risk and was addressed in the relevant section of the binimetinib RMP. This risk was removed from the list of safety concerns of binimetinib in the last approved version of binimetinib RMP (Version 2.0; dated on 24 Apr 2020) in line with the approach of the revised GVP Module V (Rev 2) as rhabdomyolysis and CK elevation are identified as ADRs for binimetinib and they are well addressed in the binimetinib SmPC. The impact to the individual is expected to be low considering the seriousness of the advanced cancer.

Impaired cardiovascular function or clinically significant cardiovascular diseases

Reason for exclusion: Left ventricular dysfunction (LVD) is a known adverse effect of MEK inhibitors including binimetinib. Due to the risk of serious worsening of left cardiac dysfunction, patients with impaired cardiac function (LVEF<50%) were excluded from clinical trials. In the pivotal PHAROS study for the NSCLC indication, the exclusion criteria remained very similar, but more precise and specific wording was applied considering an older population in NSCLC setting (and thus, potentially greater risk of cardiac dysfunction) compared with the melanoma population. As such, the term "congestive heart failure requiring treatment (Grade ≥ 2)" was used in this exclusion criterion for the PHAROS study instead of "symptomatic chronic heart failure" that was used in the studies for the melanoma indication.

Is it considered to be included as missing information? No

Rationale: Use in patients with reduced cardiac function (LVEF <50%) or symptomatic chronic heart failure was considered as a missing information for binimetinib. This risk was removed from the list of safety concerns of binimetinib in the last approved version of binimetinib RMP (Version 2.0; dated on 24 Apr 2020) in line with the approach of the revised GVP Module V (Rev 2) as specific recommendations for monitoring and management of left ventricular dysfunction are well addressed in the binimetinib SmPC, and considered as routine risk minimisation measures.

Left ventricular dysfunction is a known class-effect of MEK inhibitors. Patients with reduced cardiac function have not been included in clinical trials with binimetinib. However, if it is known that patients with reduced cardiac function or symptomatic chronic heart failure have a different safety profile to the general population for which binimetinib is indicated, any risk to these patients should be satisfactorily minimised through routine risk minimisation measures. The impact to the individual is deemed minor considering the seriousness of the advanced cancer.

History of Gilbert's syndrome

Reason for exclusion: Gilbert's syndrome is characterised by mild unconjugated non-haemolytic hyperbilirubinemia, which does not lead to hepatic inflammation, fibrosis, chronic liver disease or liver failure. Almost 100 years after its clinical description, it was linked to a genetic variant of the human bilirubin UDP-glucuronosyltransferase (*UGT1A1)*, *UGT1A1 *28*, found in approximately 40% of Caucasoid individuals (Stassburg 2008).

The main route of hepatic transformation of binimetinib is glucuronidation. The use of binimetinib in patients with Gilbert's syndrome has not been studied.

Is it considered to be included as missing information? No.

Rationale: Gilbert's syndrome is primarily linked to *UGT1A1*28* variants, but other variants in the promoter and coding regions are also involved in the predisposition of the disease (Kadakol 2000). To date, more than 100 variants have been identified in the *UGT1A1* gene (Takano 2017). Among these polymorphisms, the clinically important variants include UGT1A1*28 allelic variant (Udomuksorn 2007).

Binimetinib is primarily metabolised through UGT1A1 mediated glucuronidation, however, in clinical study sub-analysis, there was no apparent relationship observed between binimetinib exposure and UGT1A1 mutation status. In addition, simulations to investigate the effect of 400 mg atazanavir (UGT1A1 inhibitor) on the exposure of 45 mg binimetinib predicted similar binimetinib C_{max} in the presence or absence of atazanavir. Therefore, the possible extent of drug interactions mediated by UGT1A1 is minimal, and likely not clinically relevant.

There is a theoretical risk of overexposure in patients with impairment of glucuronidation in Gilbert's syndrome. However, the population PK analysis (Study CP16-001) suggests no substantial difference in binimetinib clearance in patients with UGT1A1 *28/*28 genotype compared to those without this genotype.

History or current evidence of retinal vein occlusion (RVO) or current risk factors of RVO

Reason for exclusion: RVO is a known class effect with MEK inhibitors including binimetinib. There is concern that patients with history of RVO or risk factors for RVO may be at higher risk of RVO during treatment.

Is it considered to be included as missing information? No

Rationale: Retinal vein occlusion was included as an important identified risk for binimetinib and was addressed in the relevant sections of the binimetinib RMP. This risk was removed from the list of safety concerns of binimetinib in the last approved version of binimetinib RMP (Version 2.0; dated on 24 Apr 2020) in line with the approach of the revised GVP Module V (Rev 2) as the risk is

considered well addressed in the binimetinib SmPC and no additional pharmacovigilance activities or risk minimisation measures to address this risk are needed. The impact to the individual is deemed minor considering the seriousness of the advanced cancer.

▪ Binimetinib in combination with encorafenib

In the pivotal CMEK162B2301 study which included an encorafenib arm, binimetinib and encorafenib combination arm and a single-agent vemurafenib arm, most of the exclusion criteria are not specific to encorafenib, but are common to anti-cancer study drugs in the advanced/metastatic malignant disease setting or pertaining to binimetinib, but were applied to all study arms, including encorafenib arm.

The most relevant exclusion criteria in pivotal clinical studies within the development programme that are applicable to the combination (hence due to the presence of encorafenib in the combination) but not specific to binimetinib single agent, are addressed below.

The following exclusion criteria are common to combination studies in the intended indication

Any untreated CNS lesions and history of leptomeningeal metastases and symptomatic brain metastases

Reason for exclusion: No significant effects of binimetinib were observed on CNS function at doses up to 100 mg/kg in rats and 10 mg/kg in monkeys.

In addition, patients with brain/leptomeningeal metastases are generally excluded from clinical trial participation because of their shortened life expectancy associated with symptomatic brain/leptomeningeal metastases and a concern that these patients would not receive adequate exposure (due to shortened duration) the study drug, making it difficult to appropriately evaluate clinical benefit and potentially confound overall study results. However, patients with CNS lesions were not excluded from encorafenib clinical trials in melanoma providing that their CNS metastatic lesions were appropriately treated by surgery or radiotherapy. In the PHAROS study, patients with previously treated brain metastases were not excluded if they were stable for at least 28 days prior to the first dose of study treatment and neurologic symptoms have returned to baseline. Patients with untreated brain metastases were not excluded from PHAROS study if lesions were < 5 mm and were clinically stable and asymptomatic.

Is it considered to be included as missing information? No

Rationale: There is no evidence of meaningful penetration of binimetinib or **encorafenib** into the CNS, and no evident contraindication to the treatment of patients with brain metastases due to safety reasons.

History of allogeneic bone marrow transplantation or organ transplantation

Reason for exclusion: Patients with a history of prior allogeneic bone marrow or organ transplantation are usually excluded from clinical trials due to the potential risk of developing or worsening a graft versus host disease. Furthermore, patients with prior allogenic bone marrow transplantation or organ transplantation receive intensive immunosuppressive therapy and excluding them from receiving new drugs with non-fully characterised safety profile aims to protect them from additional risks of toxicities or subsequent immunosuppression and from potential drug interactions between the immunosuppressive medications and the drugs under development.

Is it considered to be included as missing information? No

Rationale: Studies have shown that patients with allogeneic haematopoietic stem cell transplantation may be at higher risk of second cancers such as melanoma. However, in these patients, full-body skin checks before transplantation and at regular intervals thereafter with early investigation of

suspicious lesions and excision are essential elements that are part of current clinical guidelines for survivorship care (Majhail 2012, DePry 2015) for early diagnosis and tumour excision. In addition, recommendations also include using adequate sun protection and avoiding excessive exposure to sunlight (Majhail 2012).

Similar observations were made in patients undergoing kidney transplantation (Vajdic 2009).

In the real-life setting, the decision to treat patients with metastatic melanoma and who undergo bone marrow or organ transplantation should be made by the treating physician based on the individual benefit-risk.

Previous or concurrent malignancy (except for adequately treated basal cell or squamous cell carcinoma of the skin), in situ carcinoma of the cervix, treated curatively and without evidence of recurrence for at least 3 years prior to the study, and other solid tumour treated curatively, and without evidence of recurrence for at least 3 years prior to study entry

In the pivotal PHAROS study for NSCLC indication, patients with concurrent or previous other malignancy within 2 years of study entry were excluded (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).

Reason for exclusion: Prior malignancies with a risk of relapse > 10% at 5 years are usually excluded from oncology clinical trials to avoid any risk that a relapse of this malignancy interferes with the interpretation of the primary efficacy endpoint of the clinical trials evaluating a new drug in a specific indication, therefore, the main aim is to exclude an important confounding factor in the interpretation of the trial end-point.

Is it considered to be included as missing information? No

Rationale: Patients with a previous malignancy who are diagnosed with metastatic melanoma or advanced NSCLC are candidates to receive binimetinib **and encorafenib therapy**. Caution should be paid to patients with prior malignancies with RAS mutations due to the potential class effect of BRAF inhibitors which may promote cutaneous and non-cutaneous malignancies associated with activation of RAS through mutation or other mechanisms. In patients with a concurrent malignancy, the decision to treat the metastatic melanoma or advanced NSCLC or the concurrent cancer first will be taken by the treating physician based on individual benefit-risk assessment.

Known positive serology for HIV, active hepatitis B, and/or active hepatitis C infection

Reason for exclusion: Active hepatitis B and /or active hepatitis C are common concurrent infections in patients with immunodeficiency who are HIV-positive. Patients with positive serology for HIV are known to receive poly-medication including drugs with potential hepatic adverse reactions and drug-drug interactions such as anti- proteases which are CYP 3A4 inhibitors and they are also at a higher risk of different drug adverse reactions. The exclusion criterion for patients with active hepatitis B and/or active hepatitis C is due to the potential impact on evaluation of safety e.g. hepatotoxicity.

Is it considered to be included as missing information? No

Rationale: Liver laboratory parameters have been closely monitored throughout the clinical programme. Although transaminase elevations are considered to be an ADR, there is no evidence for an important identified risk. In the real-life setting, for patients diagnosed with metastatic melanoma or advanced NSCLC, the decision to treat metastatic melanoma or advanced NSCLC in patients with known positive serology for HIV, active hepatitis B, and/or active hepatitis C infection should be made by the treating physician taking into account the individual benefit-risk.

Impairment of gastrointestinal function

Reason for exclusion: Patients with impaired gastrointestinal function including active ulcerative disease, uncontrolled nausea, vomiting, diarrhoea and malabsorption syndrome were excluded due to potential unreliable administration (missed doses) and impaired absorption of the oral study drug in addition to the impact on evaluation of gastrointestinal toxicity.

Is it considered to be included as missing information? No

Rationale: In the real-life setting, the decision to treat patients with known impaired gastrointestinal function who are diagnosed with metastatic melanoma should be made by the treating physician based on the individual benefit-risk.

Gastrointestinal toxicity (diarrhoea, nausea, vomiting) is generally manageable in routine medical practice in oncology, by medical therapy and fluid electrolyte replacement and dose adjustment. No prophylaxis was required during clinical trials.

Known acute or chronic pancreatitis

Reason for exclusion: Pancreatitis or asymptomatic amylase/lipase elevations have been reported with BRAF inhibitors. For a safety evaluation of pancreas-related events, patients with known acute or chronic pancreatitis were excluded from the studies to avoid confounding factors in relation to these pre-existing conditions. This exclusion criterion was considered necessary due to the potential impact on the evaluation of pancreatic toxicity. Patients with known acute or chronic pancreatitis were however not excluded in the phase III pivotal CMEK162B2301 study for Combo 450 (the first and only encorafenib/binimetinib combination study to do so).

Is it considered to be included as missing information? No

Rationale: Although pancreatitis is a known BRAF-related effect, in the real-life setting, patients with a medical history of acute or chronic pancreatitis and who are candidates for treatment of metastatic melanoma and advanced NSCLC are monitored as per routine clinical practice and informed (via product information) that pancreatitis may occur with encorafenib administration.

Women of child-bearing potential, unless using highly effective methods of contraception, and pregnant or lactating women

Reason for exclusion: There are no data regarding the use of binimetinib in pregnant women. However, studies in animals have demonstrated reproductive toxicity.

In accordance with the ICH S9 guideline, *Nonclinical Evaluation for Anticancer Pharmaceuticals*, March 2010, fertility studies were not conducted, however no concerns were raised in repeat-dose toxicity studies in animals.

Is it considered to be included as missing information? No

Rationale: Based on the non-clinical data, reproductive toxicity (Embryo-foetal toxicity) was an important potential risk and was addressed in the relevant binimetinib RMP sections. However, this risk has been removed from the list of safety concerns of binimetinib in the last approved RMP (Version 2.0; dated on 24 April 2020) in line with the approach of the revised GVP Module V (Rev 2) as the risk is considered well addressed in the SmPC. The impact to the individual is deemed minor considering the seriousness of the advanced cancer.

Given the median age of the target population for women is over 50 years, the recommendation for effective contraception for women of childbearing potential and the severity of the disease, the use of binimetinib in pregnant or lactating women is limited.

In cases of a need for breastfeeding during treatment, the decision should be made whether to discontinue breastfeeding **encorafenib** or to discontinue treatment taking into account the benefit of breast-feeding for the child and the benefit of the drug for the mother.

Paediatric population

Reason for exclusion: No patients <18 years of age were treated in any trial in the binimetinib clinical development programme.

Is it considered to be included as missing information? No

Rationale: The paediatric population is not the target indication.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

- **Binimetinib single agent**

Table SIV.1: Binimetinib: Limitations for detecting adverse drug reactions (ADRs)

Ability to detect adverse reactions	**Limitation of trial programme**	**Discussion of implications for target population**
Rare adverse reactions	A total of 566 patients received single-agent treatment presented in the pooled Broad Safety Set. For N = 566, the 95% confidence interval to 1 ADR is [95% CI: 0.0000, 0.0052]*. This safety database would not allow an ADR that occurs with a true frequency of ≤1% to be ruled out.	The clinical development programme is unlikely to detect rare adverse reactions (frequency ≥1/10,000 to <1/1,000). Limited impact for binimetinib single agent and no intended indication for binimetinib monotherapy. When binimetinib is used in combination with encorefenib, if encorafenib is temporarily interrupted or discontinued, binimetinib is simultaneously interrupted or permanently discontinued.
Due to prolonged exposure	As of 09 November 2016, the mean (SD) duration of exposure was 18.0 (21.1) and 18.9 (19.5) weeks in the Broad and Bini 45 P Safety Sets, respectively. In the Broad Safety Set, treatment exposures ≥24 and ≥48 weeks were reported for 22.8% and 6.9% of patients, respectively. The duration is limited due to the expected early progression of disease in the study population.	Limited impact for binimetinib single agent and no intended indication for binimetinib monotherapy. When binimetinib is used in combination with encorefenib, if encorafenib is temporarily interrupted or discontinued, binimetinib is simultaneously interrupted or permanently discontinued.
Due to cumulative effects	Duration of exposure, hence cumulative dose, was limited due to expected early progression of disease in the study population.	Limited impact for binimetinib single agent and no intended indication for binimetinib monotherapy. When binimetinib is used in combination with encorefenib, if encorafenib is temporarily interrupted or discontinued, binimetinib is simultaneously interrupted or permanently discontinued.
Which have a long latency	Duration of exposure was limited due to expected early progression of disease in the study population.	Limited impact for binimetinib single agent and no intended indication for binimetinib monotherapy. When binimetinib is used in combination with encorefenib, if encorafenib is temporarily interrupted or discontinued, binimetinib is simultaneously interrupted or permanently discontinued.

**: estimated as per FDA and SmPC Guidelines*

- **Binimetinib in combination with encorafenib**

Table SIV.2: Binimetinib and encorafenib combination: Limitations for detecting ADRs

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Rare adverse reactions	The combination of encorafenib plus binimetinib has been evaluated in 372 patients with metastatic melanoma and advanced NSCLC at the recommended doses of 45 mg BID binimetinib and 450 mg QD encorafenib. Based on the 372 patients of the pooled integrated safety population (ISP), ADRs with a true frequency ≥ 1/1000 could be detected. For N=372 and event=1, the 95% [CI=0.0000, 0.0079]*, the safety database would allow an ADR that occurs with a true frequency of 1% to be ruled out.	The clinical development programme is unlikely to detect rare adverse reactions (frequency ≥1/10,000 to <1/1,000). Detection and evaluation of rare adverse reactions is part of routine post-marketing pharmacovigilance activities.
Adverse reactions due to prolonged exposure	Among all patients in the ISP and broad combination safety set, the mean (SD) duration of exposure to binimetinib combined with encorafenib was 60.0 (42.3) weeks and 53.3 (43.4) weeks, respectively, with half of patients (50.3%) in the Combo 450 ISP population and 231 (43.5%) patients in the broad population exposed to the combination for ≥48 weeks. The duration was limited, due to the expected early progression of disease in the studied population.	Limited impact for the combination. Exposure in real-life situations is not expected to be longer than in clinical trials.
Adverse reactions due to cumulative effects	Duration of exposure, hence cumulative dose, was limited due to expected early progression of disease in the studied populations.	Limited impact for the combination. Cumulative effects in real-life situations in the melanoma and NSCLC indications are not expected to be greater than in clinical trials as duration of exposure is not expected to be longer.
Adverse reactions with long latency	Duration of exposure was limited due to expected early progression of disease in the studied populations.	Limited impact for the combination. Patients with BRAF-mutant unresectable or metastatic melanoma and advanced NSCLC have a limited life expectancy, hence effects with long latency are unlikely to be relevant in the real-life setting.

* *estimated as per FDA and SmPC Guidelines.*

SIV.3 Limitations with respect to populations typically under-represented in clinical trial development programmes

Lists of populations included but under-represented (≤5% of patients exposed) or excluded in clinical trial development programmes are provided below.

Table SIV.3: Binimetinib and encorafenib combination: Exposure of special populations included or not in clinical trial development programmes

Type of special population (any included in pre-authorisation clinical development programme Yes/No)	**Persons**	**Patient-months**
Pregnant or breastfeeding women	No pregnant or breastfeeding women were enrolled or accidentally exposed to the binimetinib and encorafenib combination in clinical trials[a]	NA

Sources: Binimetinib Investigator's Brochure; version of May 2023
[a] As of 20 January 2023, a total of approximately 3627 participants have received at least 1 dose of binimetinib, either as a single agent or in all combination studies

- **Binimetinib single agent**

The duration of exposure in special populations within the Broad Safety Set (all cancers, binimetinib any dose) and the Bini 45 P safety set (all melanoma, binimetinib 45 mg) is presented in Table SIV.4.

Table SIV.4: Exposure in special populations

	All Cancers Binimetinib Any Dose (N=566)		**All Melanoma Bini 45 P (N=427)**	
	Patients n (%)	**Patient-months**	**Patients n (%)**	**Patient-months**
Baseline hepatic impairment				
Moderate	2 (0.4)	2.1	0	0
Severe	0	0	0	0
Baseline renal impairment				
Severe (CrCl<30 mL/min)	0	0	0	0
Baseline LVEF dysfunction risk factor				
Yes	22 (3.9)	98.8	22 (5.2)	98.8
Patients with history or evidence of RVO or with risk factors for RVO				
Yes	9 (1.6)	31.1	7 (1.6)	27.7
Patients with a disease severity/general condition different from inclusion criteria in clinical trials: ECOG grade 2 to 4				
Yes	7 (1.2)	17.6	5 (1.2)	13.6
Population by race				

	All Cancers Binimetinib Any Dose (N=566)		**All Melanoma Bini 45 P (N=427)**	
	Patients n (%)	**Patient-months**	**Patients n (%)**	**Patient-months**
Asian	31 (5.5)	129.2	7 (1.6)	21.3
Black (African and African American)	7 (1.2)	37.0	0	0
Other (Native Americans or Other)	5 (0.9)	5.5	2 (0.5)	3.9
Other specific populations				
Pregnant or breastfeeding women	0 (excluded from the clinical trial programme)			
Baseline uncontrolled severe hypertension	0 (excluded from the clinical trial programme)			
Baseline LVEF dysfunction< 50%, and symptomatic heart failure	0 (Excluded from the clinical trial programme)			
Immuno-compromised patients	Patients with HIV positive serology were excluded from the clinical trial programme. Patients with history of allogeneic bone marrow transplantation or organ transplantation were excluded from the clinical trial programme.			
Gilbert's syndrome	Excluded from the clinical trial programme			
Subpopulations carrying known and relevant genetic polymorphisms				
Binimetinib arm in Study CMEK162A2301, UGT1A1 Polymorphisms:				
Genotype *1/*1	N=106, 49.1% of patients; TA6/TA6 wild-type reference			
Genotype *1/*28	N=90, 41.7% of patients ; TA6/TA7 mutant			
Genotype *28/*28	N=18, 8.3% of patients ; TA7/TA7 mutant			
Genotype *36/*1	N=1, 0.5% of patients			
Genotype *36/*28	N=1, 0.5% of patients			

Sources: Tables M5.3.5.3 RMP1-7, Table M5.3.5.3 RMP1-8, Table M5.3.5.3 3.1 and Table M5.3.5.3 3.2
Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375.

For exposure in patients with hepatic and renal disorders, an extended analysis was performed taking into account the population PK analysis and dedicated studies (a summary is provided below). No pregnant or breastfeeding women were enrolled or accidentally exposed in clinical trials. No other relevant special populations have been identified.

The PK of binimetinib in patients with hepatic impairment versus healthy subjects was investigated in Study CMEK162A2104. This study included patients with mild (6 patients), moderate (6 patients), and severe hepatic impairment (5 patients). Similar exposures were observed in patients with mild impairment (total bilirubin >1 and ≤1.5×ULN and any AST value, or total bilirubin ≤ULN and AST>ULN) and subjects with normal liver function (total bilirubin ≤ULN and AST≤ULN). A two-fold

increase in total binimetinib exposure (AUC) was observed in patients with moderate (total bilirubin >1.5 and ≤3×ULN and any AST value) and severe (total bilirubin levels >3.0×ULN and any AST value) hepatic impairment. Similar conclusions can be reached when comparing the impact of hepatic impairment according to the Child-Pugh score. Model-predicted unbound binimetinib exposures are approximately 3-fold higher in both moderate and severe hepatic impairment groups. Based on these results, a dose reduction to 15 mg BID binimetinib should be recommended for patients with moderate and severe hepatic impairment. However, as encorafenib is not recommended in patients with moderate (Child Pugh B) and severe hepatic impairment (Child Pugh C), administration of binimetinib is not recommended in these patients.

Binimetinib undergoes minimal renal elimination. Six patients with severe (eGFR ≤29 mL/min/1.73 m^2) renal impairment were included in Study Array-162-106. It was shown that patients with severe renal impairment had a 29% exposure increase (AUC_{inf}), a 21% C_{max} increase, and a 22% reduced clearance resulting in longer $t_{1/2}$ of 11.2 hours vs 9.16 hours compared to matching healthy subjects. These differences were within the variability observed for these parameters in both cohorts of this study (25% - 49%) and the variability previously observed in patient clinical trials; hence these differences are unlikely to be clinically relevant. It was concluded that no dose adjustment is required for patients with renal impairment.

In Study CMEK162A2301, subgroup analyses were performed on a Japanese population (known UGT1A1 polymorphisms) to evaluate changes in steady state binimetinib exposure. The genotype of UGT1A1 was obtained for each patient to determine if the genotype influenced binimetinib exposure. As presented in Table SIV.4 above, in the binimetinib arm, most patients were of genotype *1/*1 or *1/*28. Pre-dose concentration at steady state was analysed by UGT1A1 genotype. Overall, there was no meaningful change in pre-dose concentration of binimetinib at steady state by UGT1A1 genotype.

- **Binimetinib in combination with encorafenib**

Table SIV.5: Binimetinib and encorafenib combination: Limitations with respect to under-represented populations in the integrated combination safety pool (Combo 450 ISP)

Type of special population (Any included in pre-authorisation clinical development program) Combination integrated safety population (Combo 450 ISP; N=372)				
			Patient-Persons	**months**
Patients with relevant comorbidities:	Hepatic Impairment*	Moderate	2	33.6
		Severe	0	0
	Renal Impairment	Moderate (CrCl ≥30 and ≤50mL/min)	14	140.6
		Severe (CrCl<30mL/min)	0	0
	Cardiac Impairment	Baseline LVEF Dysfunction <50%	1	8.7
Patients with a disease severity different from inclusion criteria in clinical trials:		ECOG PS ⩾ 2	1	12.0
Population with relevant different ethnic origin:		Asian	13	165.5
		Black or African American	3	4.9
		Other[1]	5	79.1
		Unknown[2]	4	21.0

Sources: ISS_Part1_u: table 1.5.1.1.5c
Sources: W00090_NSCLC - Version date: 31MAY2023 13:50 - File Name: Sub5_1_5_c1_RMPexpSpePop_treat_t.rtf

Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_1_5_c1_RMPexpSpePop_treat_t.sas 04MAY2023 11:16
Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient. Duration of exposure is defined as the max exposure between Encorafenib and binimetinib. Duration of Exposure = (date of last exposure to study drug - date of first exposure to study drug +1)/30.4375
* Hepatic impairment calculated based on NCI definition.
[1] In this table, the 'other' group does not include 'Black' origin
[2] Patients with missing value or with value equal to 'Not reported due to confidentiality reason' were included in the unknown category
Pregnant women and breastfeeding women were excluded from the trials.
No black patients were included in the pool of melanoma indication.

Table SIV.6: Binimetinib and encorafenib combination: Limitations with respect to under-represented populations in the pooled combination safety pool (Combo broad population)

Type of special population (Any included in pre-authorisation clinical development program) **Broad combination integrated safety population (Combo broad ISP; N=531)**				
			Persons	**Patient-months**
Patients with relevant comorbidities:	Hepatic Impairment*	Moderate	2	33.6
	Renal Impairment	Moderate (CrCl ≥30 and ≤50mL/min)	17	183.5
		Severe (CrCl<30mL/min)	0	0
	Cardiac Impairment	Baseline LVEF Dysfunction <50%	2	8.8
Patients with a disease severity different from inclusion criteria in clinical trials:		ECOG PS: 2 and over	7	34.66
Population with relevant different ethnic origin:		Asian	15	185.1
		Black or African American	3	4.9
		Other[1]	10	146.6
		Unknown[2]	4	20.9

Sources: ISS_Part1_u: table 1.5.1.1.5d
Sources: W00090_NSCLC - Version date: 31MAY2023 13:54 - File Name: Sub5_2_5_c1_RMPexpSPop_PHtreat_t.rtf
*Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_5_c1_RMPexpSPop_PHtreat_t.sas 10MAY2023 10:31*Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.
* Hepatic impairment calculated based on NCI definition.
[1] 1 In this table, the 'other' group does not include 'Black' origin
[2] Patients with missing value or with value equal to 'Not reported due to confidentiality reason' were included in the unknown category
Pregnant women and breastfeeding women were excluded from the trials.
No black patients were included in the pool of melanoma indication

Part II: Module SV - Post-authorisation experience of binimetinib

SV.1 Post-authorisation exposure

The International Birth Date of binimetinib is 27 June 2018.

Binimetinib was first approved in the USA on 27-Jun-2018 in combination with encorafenib for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation.

Binimetinib was approved for marketing in the EU, in the same indication on 20-Sep-2018. As of 26 June 2023, which is the DLP of the most recent Periodic Benefit-Risk Evaluation Report (PBRER/PSUR, 27-Jun-2022 to 26-Jun-2023) submitted to EMA, binimetinib has received marketing authorisation for use in 62 countries.

SV.1.1 Method used to calculate exposure

The worldwide marketing experience is estimated based on the number of tablets sold. The estimated exposure is calculated by dividing the estimated number of total tablets sold by 6 (which is the number of dosage units taken daily based on the approved prescribing information) for binimetinib, and further divided by 365.25 to obtain patient-years.

SV.1.2 Exposure

Cumulatively, the worldwide exposure to binimetinib is estimated to be 15,807 patient-years, including 8,505 patient-years in the EU countries.

From the post-marketing experience sources, no safety concern was identified in special situations including off-label use, overdose or use in special populations.

Part II: Module SVI - Additional EU requirements for the safety specification of binimetinib

Potential for Misuse for Illegal Purposes

None for binimetinib based on non-clinical data.

Given the nature of binimetinib as an anti-cancer agent, it is considered that there is an extremely low potential for abuse. There are no significant observed psychiatric or euphoric effects associated with the product which could potentially motivate its abuse potential. In rat and monkey studies there were no significant CNS effects observed. Whole-body autoradiography studies in rats found no meaningful CNS penetration. Therefore, it is not anticipated that binimetinib would be associated with any significant potential for abuse.

Part II: Module SVII - Identified and potential risks of binimetinib

- **Binimetinib single agent**

As indicated in Part II: Module SIII above, for the clinical trial exposure of single-agent binimetinib in patients with unresectable or metastatic melanoma:

- The binimetinib safety set (N=427), the 'Bini 45 P population', includes pooled data from 2 clinical studies (CMEK162A2301 [Phase III] and CMEK162X2201 [Phase II]), in which patients with metastatic melanoma (including *NRAS* mutation-positive and *BRAF*-mutation positive) were treated with single agent binimetinib at the recommended dose of 45 mg BID.
- The broad safety set (N=566), includes pooled data from 4 clinical studies in patients with advanced solid tumours treated with single agent binimetinib at doses from 30 mg BID to 80 mg BID, including patients with melanoma (*NRAS* mutation Q61positive and *BRAF* mutationpositive)

- **Binimetinib in combination with encorafenib**

As indicated in Part II: Module SIII above, safety data from 6 supportive clinical trials in patients with unresectable or metastatic melanoma and advanced NSCLC are included in this submission for the combination of binimetinib and encorafenib for the treatment of patients with unresectable or metastatic BRAF V600-mutant melanoma and BRAF V600E-mutant advanced NSCLC. Safety data from 4 clinical studies are pooled (Studies CMEK162B2301, CLGX818X2109, CMEK162X2110 and ARRAY 818-202 (C4221008)) to assess the safety of the combination at the approved doses binimetinib 45 mg BID and encorafenib 450 mg QD.

In the pooled safety analyses:

- 'Combo 450' refers to the combination of encorafenib 450 mg QD and binimetinib 45 mg BID in Study CMEK162B2301 (N=192). When appropriate, to avoid confusion with other populations, this population is referred to as Combo 450 arm of study CMEK162B2301.
- 'Combo 450 RP' (as named in the initial MAA) or the 'Melanoma population' (as named in the MAA for NSCLC indication) refers to the restricted combination safety pool for patients who received doses of encorafenib at 450 mg QD in combination with binimetinib at 45 mg BID (N=274).
- 'Combo BP for melanoma' refers to the broad combination safety pool for patients who received doses of encorafenib ranging from 400 mg to 600 mg QD in combination with binimetinib at 45 mg BID (N=433).

- 'NSCLC population' includes the patients with BRAF V600E mutant advanced NSCLC enrolled in the PHAROS study and received doses of encorafenib at 450 mg QD in combination with binimetinib at 45 mg (N=98)

- 'Integrated safety population' (Combo 450 ISP) refers to 372 patients, including 98 patients with BRAF V600E mutant advanced NSCLC enrolled at a dose of 45 mg BID binimetinib plus 450 mg QD encorafenib from PHAROS study, referred to as the 'NSCLC population', plus 274 patients with BRAF V600 mutant metastatic melanoma enrolled at or randomised to a dose of 45 mg BID binimetinib plus 450 mg QD encorafenib (192 patients from Study CMEK162B2301, 75 patients from Study CLGX818X2109 and 7 patients from Study CMEK162X2110), referred to as the 'Melanoma population (Combo 450 RP)'.

- 'Combo broad integrated safety population' includes the 'Combo BP for melanoma' (as defined above) (N=433) plus the 98 patients with BRAF V600E mutant advanced NSCLC enrolled in the PHAROS study who received binimetinib 45 mg BID in combination with encorafenib 450 mg QD; (N= 531).

SVII.1 Identification of safety concerns in the initial RMP Submission

This section is locked as per the guidance on the format of the risk management plan accompanying the GVP Module V Revision 2 (dated 31 October 2018).

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

This section is locked as per the guidance on the format of the risk management plan accompanying the GVP Module V Revision 2 (dated 31 October 2018).

- **<u>Binimetinib single agent</u>**
  - Peripheral oedema
  - Dropped head syndrome
  - Myopathy
  - Severe dermatologic reactions
  - Gastrointestinal reactions (diarrhoea, nausea, vomiting)
  - Interaction of binimetinib with P-gp and BCRP substrate inhibitors
  - Use in patients with Gilbert's syndrome

Reason for not including an identified or potential risk in the list of safety concerns for binimetinib in the RMP:

(i) Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)

Peripheral oedema

<u>Seriousness and frequency:</u>

In melanoma patients in the Bini 45 P population (N=427), Grade 3/4 AEs and SAEs of oedema were reported for 4 (0.9%) and 2 (0.5%) patients, respectively. Dose modifications (6.8% of patients) and study drug discontinuations due to oedema events (1.2% of patients) were rare (ISS Table RMP-2-2-11). AEs of oedema were reported for 201 (47.1%) patients (ISS Table RMP-2-2-11). Oedema

events were primarily Grade 1/2 in severity, with <1% of patients reporting a Grade 3/4 events (ISS Table RMP-2-2-11).

Risk/benefit impact:

Peripheral oedema is a known very common MEK inhibitor-related adverse effect. Cases were mostly non-serious and manageable. Review of listings for an association between peripheral oedema and left ventricular dysfunction showed no clear relationship. There was no impact on the risk/benefit profile in relation to the severity of the indication treated.

Dropped head syndrome

Dropped head syndrome, a class effect of MEK inhibitors, is a weakness of the neck extensor muscles due to a focal myopathy which can occur with binimetinib single agent. There are currently few reports of an association between MEK inhibitors and dropped head syndrome. Three case report publications are available. Three patients treated with selumetinib developed dropped head syndrome all of whom recovered after treatment discontinuation (Chen 2012). One patient treated with cobimetinib who recovered after dose interruption, continued treatment with a reduced dose (Gauci 2017), and another patient treated with trametinib (Kleemann 2018).

Seriousness and frequency:

A clinical review was performed across the pooled studies (N=566) to identify patients with events of dropped head syndrome. Reversible Grade 1/2 neck muscle weakness was reported in 3 patients in clinical trials. Reversible neck muscle weakness despite continuation of binimetinib therapy was reported as Grade 1 dropped head syndrome in 2 patients of Asian ethnicity treated with 45 mg BID in Study CMEK162X1101. One of these patients had two episodes. No dose modification was undertaken. In addition, two serious cases were reported. One patient treated with binimetinib 45 mg QD in Study CMEK162A2301 experienced serious dropped head syndrome after 20 months on treatment, with mild CK elevations (Longvert 2018). Treatment was interrupted, and the patient recovered rapidly. Treatment was re-started at a reduced dose of 30 mg BID. Mild dropped head syndrome occurred but was stable for 10 months without any need for dose modification. Another patient in Study CMEK162A2301 experienced Grade 2 dropped head syndrome after 18 months of study treatment (after the cut-off date of 18 March 2016), with concomitant grade 2 CK elevation while receiving a reduced dose for an unreported reason. The event worsened 3 months later to grade 3 which was reported as an SAE. Mild CK elevation was noted. Binimetinib was permanently discontinued and the patient recovered rapidly.

Risk/benefit impact:

A limited impact on the risk/benefit profile is expected. Very few cases of dropped head syndrome with binimetinib have been identified in the Broad Safety Set, and all were reversible.

Myopathy

Seriousness and frequency:

In the binimetinib arm of Study CMEK162A2301, events with the PT of myopathy were reported in 1 (0.4%) patient (Grade 3/4: no patients). In the binimetinib arm of Study CMEK162A2301, no SAEs with the PT of myopathy were reported (ISS Table RMP 2.2-10).

In melanoma patients in the Bini 45 P population (N=427), *myopathy* events (AESI grouping) were reported 15.5% of patients. Few events were Grade 3/4 (2.3%), were serious (0.5%) or led to study drug discontinuation (1.2%). A limited number of events required dose adjustment (4.7%) or required additional therapy (2.6%). The most frequent PT was *myalgia* (9.8%). In the Bini P population, the other PTs reported were *muscular weakness* (6.3%) and *myopathy* (0.2%) (ISS-PART1-U Table 2.1.12.1-u, Table 2.1.12.2-u and Table 2.1.12.3-u).

Risk/benefit impact:

A limited impact on the risk/benefit profile is expected; generally mild and moderate (Grade 1 and 2) events have been observed.

Severe dermatologic reactions

Seriousness and frequency:

In melanoma patients in the Bini 45 P population (N=427), all grade overall rash AEs (including rash, acneiform dermatitis, macular rash, maculo-papular rash, generalised rash and pustular rash) were reported in 82.7% of patients, including acneiform dermatitis in 41.5% and skin infections in 17.3% of patients.

Grade 3-4 overall rash and skin infection AEs were reported in 6.8% and 4.7% of patients respectively (ISS-Part 1_u Table 2.1.1.1-u, Table 2.1.1.2-u, Table 2.1.1.3-u; ISS Table 2.1.2.1-u, Table 2.1.2.2-u and Table 2.1.2.3-u). Rash and skin infections SAEs were reported in 0.7 %and 3.7% of patients respectively.

Dose modifications due to rash events were reported in 15.2% and study drug discontinuations were reported 2.3% of patients. Additional therapy was reported in 68.1% of patients. Dose modifications due to skin infections occurred in 4.2% of patients and no patients discontinued study drug due to skin infections. Additional therapy was reported in 15.0%.

Of note, skin toxicities were reported with significantly lower incidences and lower severity in patients treated with binimetinib in combination with encorafenib compared to patients who received binimetinib single agent at the recommended dose.

In melanoma patients treated at the recommended dose of binimetinib and encorafenib (Combo 450 RP, N=274) all grade rash AEs (including rash, acneiform dermatitis, macular rash, maculo-papular rash, generalised rash and pustular rash), acneiform dermatitis and skin infections were reported in 24.5%, 3.6% and 12.8% of patients respectively. Grade 3-4 rash and skin infections AEs were reported in 0.7% and 1.5% of patients respectively.

When considering the exposure adjusted incidences, EAIR were 2.19 vs 110.72 patient-months for Combo 450 vs binimetinib for rash events and 1.03 vs 4.60 patient-months respectively for skin infections (Source ISS-Part 1_u Table 2.1.1.1-u, Table 2.1.1.2-u, Table 2.1.1.3-u; ISS Table 2.1.2.1-u, Table 2.1.2.2-u and Table 2.1.2.3-u).

Risk/benefit impact:

Skin toxicities including rash (various types), acneiform dermatitis and skin infections are known common MEK inhibitor-related adverse reactions. Incidences of skin events were significantly decreased in the combination and appeared as meaningfully attenuated by the combination with encorafenib BRAF inhibitor. Those events were mostly low grade, nonserious and manageable and required significantly less dose modification and/or additional therapy compared to events reported in the binimetinib single agent population. This attenuated toxicity may be explained by the reduction of paradoxical activation of the ERK pathway by simultaneous MEK inhibition (Torti 2012). Given that binimetinib use is not intended for use as a single agent. If encorafenib is temporarily interrupted or discontinued in the combination due to adverse reactions, binimetinib should also be interrupted or discontinued, and patients should not be exposed to binimetinib single agent, thus no anticipated impact on the risk/benefit profile in relation to the severity of the indication treated is anticipated.

(ii) Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated

None.

(iii) Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are

adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised

Gastrointestinal reactions (diarrhoea, nausea, vomiting)

Seriousness and frequency:

In the binimetinib arm of Study CMEK162A2301, gastrointestinal events (based on adverse event of special interest (AESI) grouping) were reported in 65.1% (CI 59.03, 70.75) of patients (ISS Table RMP 2.2-1). Events reported most commonly by PT were diarrhoea (40.1% of patients), nausea (30.1% of patients) and vomiting (21.6% of patients).

In the binimetinib arm of Study CMEK162A2301, SAEs were reported in 3.3% of patients and included the PTs of vomiting (1.1% of patients), diarrhoea and nausea (0.7% of patients each) (ISS Table RMP 2.2-1).

In the Bini 45 P population, diarrhoea (diarrhoea, frequent bowel movements PTs) occurred in 182 patients (42.6%), with 1.9% Grade 3 events; 0.5% discontinued, 5.6% required dose adjustment or study drug interruption, and 14.8% required additional therapy. Nausea occurred in 128 patients (30%) with 1.2% Grade 3 events; 0.5% discontinued, 4.2% required dose adjustment or study drug interruption and 12.6% required additional therapy. Vomiting (vomiting, retching PTs) occurred in 86 patients (20.1%) with 1.9% Grade 3 events; 0.7% discontinued Bini 45 mg due to vomiting and 4.4% patients required dose adjustment or study drug interruption and 6.1% required additional therapy (ISS-Part 1_u Table 2.6.1.2a).

Risk/benefit impact:

Gastrointestinal adverse events are considered to be a class effect of MEK inhibitors, including binimetinib. A limited impact on the risk/benefit profile is expected; generally mild and moderate (Grade 1 and 2) and reversible events have been observed in the Bini 45 P. No Grade 4 gastrointestinal events were reported.

(iv) Known risks that do not impact the benefit-risk profile

None.

(v) Other reasons for considering the risks not important

Interaction of binimetinib with P-gp and BCRP substrate inhibitors

Seriousness and frequency:

No clinical data available.

Risk/benefit impact:

Binimetinib is a substrate of both P-gp and BCRP. Inhibition of P-gp or BCRP is unlikely to result in a clinically important increase in binimetinib concentrations as binimetinib exhibits moderate to high passive permeability. Therefore, the potential for in vivo drug interaction with inhibitors or inducers of P-gp and BCRP is considered to be minimal. No impact on the risk/benefit profile is expected.

Use in patients with Gilbert's syndrome

The main route of hepatic transformation of binimetinib is glucuronidation. The use of binimetinib in patients with Gilbert's syndrome has not been studied.

There is a theoretical risk of overexposure in patients with impairment of glucuronidation in patients with Gilbert's syndrome. However, the population PK analysis in the report of Study CP16-001 suggest no substantial difference in binimetinib clearance in patients with a UGT1A1 *28/*28 genotype compared to those without this genotype.

Risk/benefit impact:

The risk is not considered important in relation to the severity of the indication treated.

The decision for treatment should be made by the treating physician taking into account the individual benefit-risk of the patient.

▪ Binimetinib in combination with encorafenib

The risks not considered important for inclusion in the list of safety concerns in the RMP for encorafenib in combination with binimetinib are:

- Neutropenia
- Gastrointestinal toxicity
- Photosensitivity

Of note, non-clinical findings were predictive of potential for synergistic skin toxicity but interestingly, the known binimetinib-related skin reactions including skin infections were significantly attenuated by the combination (see Module SVII.1.1).

Reason for not including an identified or potential risk in the list of safety concerns for the combination in the RMP:

(i) Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)

Neutropenia

The following newly occurring or worsening haematology abnormalities were reported with a higher incidence (≥5% difference for any CTCAE grade) in the Combo 450 RP population than the Enco 300 P population: decreases in leukocyte count (grade 1: 12.9% vs 3.9%), decreases in neutrophil count (grade 1: 9.5% vs 3.9%) and decreases in platelet counts (grade 1: 10.1% vs 4.4%).

In the study CMEK162B2301, the incidence of treatment-emergent laboratory abnormalities (changes from baseline) occurring in ≥10% (all grades) or ≥2% (grade 3/4) of patients treated with binimetinib and encorafenib, included neutropenia in 15.1% (all grades) and 3.6% (grade 3/4). In the encorafenib 300 mg arm the incidence of neutropenia was lower, occurring in 4.7% (all grades) and 1.0% (grade 3/4) of patients.

Overall, in the Combo 450 RP population, neutropenia was reported in 11 patients with no associated symptoms. Febrile neutropenia was reported in 2 patients, and in 4 patients, neutropenia was associated with either influenza, sore throat, pharyngitis or oral herpes. No neutropenic sepsis or neutropenic severe infection was reported.

Based on the available data, the risk of neutropenia, a well-known adverse reaction in oncology practice, appears minimal in relation to the severity of the treated disease. Hence, there is no impact on the benefit-risk profile.

(ii) Known risks that do not impact the benefit-risk profile

Gastrointestinal toxicity

The ADRs nausea and vomiting were very common with higher rates in the Combo 450 RP population than the melanoma Bini 45 P population, with nausea in 41.6% and 30.0% of patients respectively, and vomiting in 28.1% and 20.1% of patients respectively. However, incidence of grade 3/4 events was similar in the two populations with nausea in 2.6% and 1.2%; and vomiting in 2.2% and 1.9%% respectively. Despite the high frequency of these gastrointestinal events, the treatment dose intensity was high, close to 100% for both agents in the combination. When adjusted to the duration

of treatment, the difference for overall nausea and vomiting is significantly reduced with EAIRs for nausea of 4.62 and 8.68 with Combo 450 RP and Bini 45 P respectively, and for vomiting of 2.59 and 5.29 respectively.

The ADR diarrhoea was reported at a similar incidence (difference<5%) in the Combo 450 RP population compared to the Bini 45 P population with 38.0% and 42.6% of patients respectively. Incidence of diarrhoea grade 3/4 events was similar also (3.3% vs 1.9%). Constipation and abdominal pain were more commonly reported in the Combo 450 population than the Bini 45 P population with constipation in 24.1% and 14.8% and abdominal pain in 27.4% vs 15.9 of patients respectively, but no impact was observed for the severe grade events (Grade 3/4 constipation in 0.0 and 0.5%; 3/4 abdominal pain in 2.6% vs 1.6% respectively).

In the Combo 450 RP population, dose adjustments were required in 7.3% of patients for nausea and in 6.2% for vomiting but no events led to treatment discontinuation. For diarrhoea, dose adjustments were required in only 4.4% of patients, and led to treatment discontinuation in 0.4% of patients.

Additional therapy was required for nausea in 20.8% of patients, for vomiting in 7.7% and for diarrhoea in 14.2%. Prophylaxis for gastrointestinal toxicity was not used in the reported clinical trials. The higher rates of diarrhoea, constipation and abdominal pain observed with the combination do not impact the benefit-risk profile.

Based on these data, the known risk of gastrointestinal toxicity of BRAF and MEK inhibitors is not considered as a safety concern in binimetinib and encorafenib combination at the recommended dose.

Photosensitivity

Preclinical photosafety assessment indicated a minimal potential risk for phototoxicity with binimetinib and a low potential risk for phototoxicity with encorafenib.

Photosensitivity (including photosensitivity reaction, sunburn and solar dermatitis PTs) is identified as an ADR for binimetinib in combination with encorafenib. Photosensitivity was reported at a low incidence in the Combo 450 RP population in 4.0% of patients. Few events were severe (Grade 3 in 0.5% of patients), required dose study drug interruption/reduction (0.5% of patients) and required additional therapy (1.8% of patients). No events were serious, or led to study drug discontinuation. In binimetinib 45 mg population, photosensitivity events were reported in 1.6% of patients. None were serious or severe (grade 3-4) or led to treatment discontinuation. Dose interruption/reduction and additional therapy were reported in 0.2% and 0.9% of patients.

In Study CMEK162B2301, photosensitivity events regardless of causality to study drugs were reported at a much lower incidence in the Combo 450 arm than in the vemurafenib arm in 4.7% vs 38.2%). Exposure adjusted incidence rate was 0.30 case per 100 patient-months vs 7.02 cases per 100 patient-months respectively. Few events were Grade 3/4 (0.5% vs 1.6%) or led to study treatment discontinuation (none vs 1.1%). Dose interruption/reduction were reported in 0.5% and 4.3% of patients. and additional therapy due to AEs in 2.6% vs 16.7% of patients in the Combo 450 and vemurafenib arms, respectively.

The risk of photosensitivity, a known BRAF inhibitor adverse effect (Zelboraf® [vemurafenib] SmPC and dabrafenib [Hauschild 2012; Mattei 2012; Ascierto 2013; Gabeff 2015; Erfan 2017]), especially for vemurafenib. Photosensitivity was observed with a high incidence (>30%) and severe events with vemurafenib use (Zelboraf® *[vemurafenib]* SmPC) and was reported in combination MEK/BRAF inhibitor therapies. For the vemurafenib and cobimetinib combination, photosensitivity was observed in 47.3% of patients with Grade 3-4 events in 4.5% of patients in the coBRIM phase III study (Dréno 2017). Photosensitivity is considered as an ADR for encorafenib single agent and in combination with binimetinib with an overall incidence rate <5%. Based on the data for encorafenib and binimetinib combination, there is no clinical evidence of enhanced toxicity due to the combination of encorafenib and binimetinib. The low incidence and severity of photosensitivity do not impact the benefit/risk profile of the combination. Photosensitivity is not considered as an important risk requiring a special warning in the SmPC for either encorafenib or binimetinib. Sun exposure being a known risk factor

for malignant melanoma, patients treated for malignant melanoma are generally advised about sun protection in routine practice, and no additional protection measure is warranted for Combo 450.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

There is no indication of binimetinib single agent. Binimetinib use is only considered in the setting of the combination with encorafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Important identified and potential risks and missing information specific to binimetinib are listed below and further detailed in the relevant section:

- Left ventricular dysfunction
- Hypertension
- Rhabdomyolysis
- Hepatotoxicity
- Retinal vein occlusion (RVO)
- Retinal pigment epithelium detachment (RPED)
- Venous thromboembolism (VTE)
- Haemorrhage
- Pneumonitis/interstitial lung disease (ILD)
- Embryo-foetal toxicity
- Over-exposure in patients with moderate to severe hepatic impairment
- Use in patients with reduced cardiac function (LVEF <50%) or symptomatic chronic heart failure

Important identified risks

Left ventricular dysfunction

Cardiac events were reported with an overall incidence of 11.9% in the Bini 45 P population, in particular events related to asymptomatic ejection fraction decrease as detected by protocol-specified ECHO/MUGA scans and cardiac failure and are a class effect of MEK inhibitors.

Left ventricular dysfunction is identified as an ADR for binimetinib.

The benefit-risk impact is limited based on the risk minimisation measures.

Please refer to Section SVII.3 for further details.

Hypertension

Hypertension (new or worsening blood pressure) was reported with an overall incidence of 15.9% in the Bini 45 P population and is considered a class-related risk for MEK inhibitors including binimetinib. Hypertension is an AE mostly occurring in patients with predisposing factors and may be serious.

Hypertension including severe hypertension is identified as an ADR for binimetinib.

The benefit-risk impact is limited based on the risk minimisation measures. Please refer to Section SVII.3 for further details.

Rhabdomyolysis

Elevated blood CK is a frequent laboratory finding associated with the administration of MEK inhibitors, including binimetinib, and it can be infrequently associated with concomitant muscular

symptoms. The binimetinib safety profile is characterised by common blood CK elevations, with or without AEs involving muscle symptoms. Reversible CK elevation has been reported across all studies with binimetinib; however, in most cases this elevation was not associated with notable clinical consequences.

Rhabdomyolysis is identified as an ADR for binimetinib. Events with the PT of rhabdomyolysis were reported in 2 (0.5%) patients in the all melanoma Bini 45 P population (N=427).

The benefit-risk impact is limited based on the risk minimisation measures.

Please refer to Section SVII.3 for further details.

Hepatotoxicity

Liver toxicity, including elevation of hepatic enzymes, is a class effect for MEK inhibitors including binimetinib. Across the clinical development programme, the most common AEs reported have been AST and ALT elevation. No case of Hy's law has been identified.

Hepatotoxicity is considered as an important identified risk for binimetinib single agent but regarded as an important potential risk in the setting of the combination therapy.

The benefit-risk impact is limited based on the risk minimisation measures.

Please refer to Section SVII.3 for further details.

Retinal vein occlusion (RVO)

RVO is a well-known MEK inhibitor-associated class effect and as an important identified risk due to its seriousness.

Retinal vein occlusion is identified as an ADR for binimetinib but was not observed for binimetinib in combination with encorafenib, therefore considered as an important potential risk for the combination. The benefit-risk impact is limited based on the risk minimisation measures.

Please refer to Section SVII.3 for further details.

Retinal pigment epithelium detachment (RPED)

Retinopathy or serous retinopathy or RPED is a well-known MEK inhibitor-associated class effect and generally actively monitored during therapy with MEK inhibitors.

Retinal pigment epithelium detachment is identified as a very common and mostly asymptomatic ADR for binimetinib but with possible visual disturbances.

The benefit-risk impact is limited based on the risk minimisation measures.

Please refer to Section SVII.3 for further details.

Venous thromboembolism (VTE)

Venous thromboembolism events have been noted to occur with treatment with MEK inhibitors, including binimetinib.

Venous thromboembolism is identified as an ADR for binimetinib. In advanced melanoma patients, although it is confounded by the role of the disease itself, this risk is considered as an important identified risk due to its potential seriousness.

The benefit-risk impact is limited based on the risk minimisation measures.

Please refer to Section SVII.3 for further details.

Haemorrhage

Haemorrhage is a known class effect of MEK inhibitors.

Haemorrhage is determined as a very common ADR, reported for various sites and considered as a safety concern due to its potential seriousness.

The benefit-risk impact is limited based on the risk minimisation measures.

Please refer to Section SVII.3 for further details.

Important potential risks

Pneumonitis/Interstitial lung disease

Pneumonitis events have been observed in the pooled studies of single-agent binimetinib in patients with advanced cancer, as well as with other MEK inhibitors.

The benefit-risk impact is limited based on the risk minimisation measures.

Please refer to Section SVII.3 for further details

Embryo-foetal toxicity

Embryo-foetal development studies showed evidence of teratogenicity in rabbits (ventricular septal defects and pulmonary trunk alterations at the highest doses) and in rats decreased ossification that is considered as secondary to decreased foetal body weight at maternally toxic doses. There are no human clinical data or events reported suggesting embryo-foetal toxicity.

Patients of reproductive potential are expected to adhere to strict contraceptive measures. Given that there are recommendations for effective contraception for women of childbearing potential and not to use binimetinib in pregnant women, the benefit-risk impact is limited against the severity of the disease.

Please refer to Section SVII.3 for further details.

Over-exposure in patients with moderate to severe hepatic impairment

In patients with moderate to severe hepatic impairment, the metabolism and elimination of binimetinib is affected. Patients with moderate to severe hepatic impairment are at risk of over-exposure to binimetinib if the dose is not adjusted accordingly. If patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment were to be treated with binimetinib, dose reduction to 15 mg BID is recommended. However, in the combination setting,as encorafenib is not recommended in patients with moderate (Child-Pugh B) or severe hepatic impairment (Child-Pugh C), administration of binimetinib is not recommended in these patients.

The benefit-risk impact is considered limited based on the risk minimisation measures and the setting of the intended therapeutic use. In the real-life setting, patients with hepatic impairment should be closely monitored for toxicities.

Please refer to Section SVII.3 for further details.

Missing information

Use in patients with reduced cardiac function (LVEF <50%) or symptomatic chronic heart failure

As discussed in Part II: Module SIV, patients with impaired cardiac function (LVEF < 50%) were excluded from the clinical trial development programme.

The effects in patients with inadequate cardiac function are unknown and binimetinib has demonstrated the potential to cause reversible cardiac dysfunction. In these patients, binimetinib should be used with caution and in the case of any symptomatic left ventricular dysfunction, grade 3-4 LVEF decrease, or absolute LVEF decrease from baseline of ≥ 10%, binimetinib should be discontinued and LVEF should be evaluated every 2 weeks until recovery.

The benefit-risk impact is considered limited based on the risk minimisation measures and the setting of the intended therapeutic use. In the real-life setting, patients with reduced cardiac function (LVEF <50%) or symptomatic chronic heart failure should be closely monitored for left ventricular dysfunction.

Please refer to Section SVII.3 for further details.

SVII.1.3. Additional risks considered important for inclusion in the list of safety concerns for binimetinib in combination with encorafenib

None.

There are no new additional safety concerns for binimetinib combination with encorafenib other than those already determined for binimetinib and addressed above.

The overall safety profile of the combination of binimetinib 45 mg BID and encorafenib 450 mg QD is consistent with the mechanisms of action and the known safety profiles of MEK and BRAF inhibitors as single agents or in combination.

The addition of binimetinib to encorafenib allowed greater exposure to encorafenib in patients treated with Combo 450 mg and interestingly attenuated certain known effects of BRAF inhibitors.

The addition of binimetinib to encorafenib was associated with a lower incidence (difference ≥10% in Enco 300 P vs Combo 450 RP) of the following ADRs associated with the BRAF inhibitor encorafenib, in particular skin disorders (PPES, rash, alopecia, pruritus, hyperkeratosis and dry skin), myalgia, arthralgia, decreased appetite, and melanocytic neavus. One case of melanoma in situ (PT new primary melanoma) was reported in the Combo 450, and fewer patients experienced cutaneous SCC and basal cell carcinoma.

The most common binimetinib-driven ADRs observed in the combination included skin reactions, ocular reactions (retinal detachment, visual impairment), cardiac dysfunction (left ventricular dysfunction), hypertension and creatinine phosphokinase elevation. Certain ADRs of the Combo 450, driven by binimetinib, are potentially serious (severe hypertension, left ventricular dysfunction, venous thromboembolism, liver laboratory abnormalities, haemorrhage, ocular events and rhabdomyolysis), and are reflected in the AEs/SAEs leading to treatment discontinuation, but were manageable with dose modifications, monitoring of left ventricular and arterial blood pressure, ophthalmological assessments and adequate clinical management with regard to individual risk factors.

The addition of binimetinib to encorafenib was associated with a numerically higher incidence of adverse events for abnormal LFTs (ALT, AST and GGT), however no case of hepatic failure or hepatitis related to binimetinib in combination use with encorafenib or no case meeting Hy's Law criteria have been reported, therefore hepatotoxicity is considered as an important potential risk for binimetinib in the combination setting.

Of note, retinal vein occlusion (RVO) determined as an important identified risk for binimetinib single agent is considered as an important potential risk for binimetinib when used in combination with encorafenib. No case of RVO has been reported in the reference safety population Combo 450 RP and RVO was not identified as an ADR for the binimetinib and encorafenib combination. No case of RVO was reported in the Combo 450 RP.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

No important identified or potential risk or missing information is re-classified, removed or added in this updated submitted version of the RMP.

SVII.3 Details of important identified risks, important potential risks and missing information

SVII.3.1 Presentation of important identified and important potential risks

(i) Important identified risk: Left ventricular dysfunction

Potential mechanisms:

Left ventricular dysfunction is a class effect for MEK inhibitors, including binimetinib. Logistic regression evaluation of Grade 2 or greater LVEF reduction and exposure found no significant relationships for increased incidence and increased exposure for model predicted exposure metrics ($C_{max,ss}$, $AUC_{tau,ss}$ and $C_{min,ss}$). This finding suggests that binimetinibinduced left ventricular dysfunction is not dose related, in the study population with no major cardiovascular disorder.

Drug-induced cardiotoxicity resulting in ventricular dysfunction has been classified into 2 distinct types. Anthracyclines are well known for causing irreversible, dose-dependent cardiotoxicity, resulting in type I chemotherapy-related cardiac dysfunction. Type I chemotherapy-related cardiac dysfunction is myocardial injury characterised by myofibrillar disarray, necrosis, and vacuoles on microscopy. Oxidative stress via free radical formation is the mechanism proposed for myocardial injury resulting in a decrease in ejection fraction with global hypokinesis. In contrast, type II chemotherapy-related cardiac dysfunction has been implicated with molecular targeted drug agents. Type II cardiac dysfunction results in no changes on ultrastructure, is not dose-dependent, and is reversible, with a favourable prognosis (Le 2014).

Binimetinib non-clinical studies have not identified cardiac concerns. In particular no histological lesions have been observed. This finding is supported by clinical observations of predominantly reversible cardiac events, suggesting that binimetinibinduced cardiac events correspond to type II cardiac dysfunction.

Evidence source and strength of evidence:

Left ventricular dysfunction is an identified ADR for binimetinib. Left ventricular dysfunction is a known effect of MEK inhibitors, a class of drugs to which binimetinib belongs. There is sufficient scientific evidence to suspect a causal association between binimetinib and this risk.

Characterisation of the risk:

Frequency with 95% CI:

In melanoma patients in the Bini 45 P population (Bini 45 P; N=427), left ventricular dysfunction, defined as symptomatic or asymptomatic decreases in ejection fraction, can occur with binimetinib. Left ventricular dysfunction, including ejection fraction decreased, was reported in 11.9% (51/427) of patients, and was Grade 3/4 in 4.4% (19/427) of patients. It was the most frequent cause of dose discontinuation, which was required in 4.2% of patients. Additional therapy was reported in 0.9% (4/427) of patients. In Study CMEK162A2301, left ventricular dysfunction reported in 14.1% of patients in the binimetinib arm.

In the binimetinib arm in Study CMEK162A2301, the most frequently reported cardiac event was ejection fraction decreased (33 [12.3%] patients) (Table RMP2.1-7, Table RMP2.2-7).

Table SVII.1: Summary of left ventricular dysfunction events (Bini 45 P)

	All Melanoma
Cardiac Events	**Bini 45 P N=427 n (%)**
Overall incidence	51 (11.9)
Related overall incidence	47 (11.0)
Grade 3 to 4	19 (4.4)
PT with incidence >10%	
Ejection fraction decreased	44 (10.3)
SAEs overall incidence	2 (0.5)
AEs leading to discontinuation	18 (4.2)
AEs leading to dose change/reduction/interruption	27 (6.3)
AEs requiring additional therapy	4 (0.9)

Sources: Table M5.3.5.3 RMP2.1-7, Table M5.3.5.3 RMP2.2-7.
A patient with multiple occurrences is counted only once with the maximum reported severity.
MedDRA Version 19.0 and (Compound Case Retrieval Strategy_Binimetinib_MedDRA 18.1_09Nov2015) have been used for the reporting of adverse events.
Events included (PTs): Diastolic dysfunction, ejection fraction abnormal, ejection fraction decreased, left ventricular dysfunction, pulmonary oedema.

In Study CMEK162A2301, Kaplan-Meier plots of time to first Grade ≥3 left ventricular dysfunction events for patients with an event showed that the median time to onset was of 1.5 months [95% CI: 0.9, 3.4]) for the Bini 45 P population.

In the Combo 450 ISP, left ventricular dysfunction (including PT: ejection fraction decreased, cardiac failure and left ventricular dysfunction) was reported in 9.4% (35/372) of patients. Grade ≥3 events were reported at a lower incidence in the Combo 450 ISP than in the Bini P population (1.3% vs 4.4%). Events requiring dose adjustment or interruption were reported in 6.2% (23/372). One event was serious (0.3%). Few events required additional therapy (1.9%), or required study drug discontinuation (0.8%). The most frequent PT was ejection fraction decreased (7.5%).

In the Combo 450 RP (Melanoma population), left ventricular dysfunction events were reported in 8.4% (23/274), and events requiring study drug dose adjustment or interruption in 6.6% (18/274). Grade≥3 events were reported in 1.1% (3/274) of patients. One event was serious (0.4%), and few events required additional therapy (2.2%), or required study drug discontinuation (0.4%). The most frequent PT was ejection fraction decreased (6.6%).

In the NSCLC population, left ventricular dysfunction events were reported in 12.2% (12/98). Grade ≥ 3 events were reported in 2.0% (2/98) patients. Events requiring study drug dose adjustment or interruption were reported in 5.1% (5/98) of patients. No event was serious. Few events required study drug discontinuation (2.0%). Event required additional therapy was reported in one patient (1.0%). The most frequent PT was ejection fraction decreased (10.2%).

In Study CMEK162B2301, in the Combo 450 arm, left ventricular dysfunction was reported in 7.8% (15/192) of patients, with the most frequently reported cardiac event ejection fraction decreased in 5.7% (11/192).

Table SVII.2: Summary of left ventricular dysfunction events (Combo 450 ISP, Combo 450 RP [Melanoma population], NSCLC population, and Combo 450 arm of Study CMEK162B2301)

	Combo 450 ISP	**NSCLC population**	**Combo 450 RP (Melanoma population)**	**Study CMEK162B2301**
Cardiac Events	**Combo 450mg QD N=372 n (%)**	**Combo 450mg QD N=98 n (%)**	**Combo 450mg QD N=274 n (%)**	**Combo 450mg QD N=192 n (%)**
Overall incidence	35 (9.4)	12 (12.2)	23 (8.4)	15 (7.8)
Related overall incidence	26 (7.0)	7 (7.1)	19 (6.9)	12 (6.3)
Grade 3+	5 (1.3)	2 (2.0)	3 (1.1)	3 (1.6)
PT with incidence ≥5%[1]				
Ejection fraction decreased	28 (7.5)	10 (10.2)	18 (6.6)	11 (5.7)
SAEs overall incidence	1 (0.3)	0	1 (0.4)	0
AEs leading to discontinuation	3 (0.8)	2 (2.0)	1 (0.4)	0
AEs leading to dose change/reduction/interruption	23 (6.2)	5 (5.1)	18 (6.6)	12 (6.3)
AEs requiring additional therapy	7 (1.9)	1 (1.0)	6 (2.2)	2 (1.0)

Sources: ISS Table 2.1.6.1, Table 2.1.6.2 and Table 2.1.6.3
Sources: W00090_NSCLC - Version date: 25JUL2023 12:19 - File Name: Sub5_3_3_c1_RMPlVentEnBi_saf_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADADR:24JUL2023 ADSP1.ADSL:27JUN2023 - PGM Sub5_3_3_c1_RMPlVentEnBi_saf_t.sas 30JUN2023 12:29
[1] PT with incidence ≥ 5% in any population.
A patient with multiple adverse events within a preferred term is counted only once in that preferred term. MedDRA Version 25.1 has been used for the reporting of adverse events.

In the post-marketing experience, cumulatively up to 26 June 2023 (DLP of the most recent PSUR), 48 cases were identified in the global safety database with 50 events (of them, 36 were serious) potentially describing left ventricular dysfunction, including the PTs: ejection fraction decreased (21 events), cardiac failure (13), cardiomyopathy (6), cardiac failure congestive, cardiogenic shock, pulmonary oedema (2 each), cardiac failure acute, cardiotoxicity, ejection fraction abnormal, and left ventricular failure (1 each). These cases represent 0.9% of all post-marketing cases in the global database. These cases concerned 12 female patients, 26 male patients while the gender was not reported in the remaining 10 cases, patients' age was between 30-84 years.

Absolute risks

The absolute risk of left ventricular dysfunction in the binimetinib single agent Bini 45 P safety pool was 0.103.

The absolute risk of left ventricular dysfunction in the binimetinib single agent Combo 450 RP was 0.084

Relative risks

In order to perform the relative risk (RR) calculations, a literature search was undertaken to identify European studies reporting the risk of cardiac ventricular dysfunction (LVD) in real-world, BRAF-mutated metastatic melanoma patients who were unexposed to binimetinib single agent or to any interventions in the same therapeutic class (i.e. any MEK inhibitor for binimetinib single agent).

No studies reporting the risk of LVD in a relevant "unexposed" patient population were identified for the purposes of the binimetinib single agent RR calculations; therefore, no RR calculations could be performed.

In order to perform the relative risk (RR) calculations, a literature search was undertaken to identify European studies reporting the risk of cardiac ventricular dysfunction (LVD) in real-world in BRAF-mutated metastatic NSCLC patients who were unexposed to binimetinib single agent or to any interventions in the same therapeutic class (i.e. any MEK inhibitor for binimetinib single agent). No studies in the relevant unexposed population were identified in this search.

No studies reporting the risk of LVD in a relevant "unexposed" patient population were identified for the purposes of the binimetinib single agent RR calculations; therefore, no RR calculations could be performed.

Seriousness:

Cardiac events (LVD) were reported as an SAE for 1 (0.4%) patient in the binimetinib arm of Study CMEK162A2301, and in a total of 2 (0.5%) patients in the melanoma Bini 45 P population (both PTs of ejection fraction decreased) (Table RMP2.2-7).

One serious event (0.4%) of left ventricular dysfunction was reported in the Combo 450 RP (Melanoma population), with no serious event in the NSCLC population. As such, one serious event of left ventricular dysfunction was reported in the Combo 450 ISP (0.3%)

No serious event was reported in Combo 450 arm of the Study CMEK162B2301.

Severity:

Of the patients with events related to LVEF decrease in Study CMEK162A2301, a clinical review showed that no patients had concurrent AEs of dyspnoea or orthopnoea reported. Nevertheless, Grade 3/4 events were reported in 19 (4.4%) and 12 (4.5%) patients in the melanoma Bini 45 P population and in the binimetinib arm of Study CMEK162A2301, respectively (Table RMP2.1-7).

Ejection fraction decreased was the AE that most frequently led to study drug discontinuation (4.1% of the patients treated with binimetinib) in Study CMEK162A2301 and was reported in 16/427 (3.7%) melanoma patients in the Bini 45 P population (Table RMP2.2-7).

In Study CMEK162A2301, for patients with an event, Kaplan-Meier plots of time to first Grade ≥3 cardiac event showed a median time to onset of 1.5 months for both the binimetinib arm of Study CMEK162A2301 and the all melanoma Bini 45 P population; however, the number of patients at risk was very small and by Month 2, there were <10 patients in each binimetinib-treated population.

For patients with an event, Kaplan-Meier plots of the median time to onset of LVEF below 50% showed an onset of 1.4 months in both the binimetinib arm of Study CMEK162A2301 and the all melanoma Bini 45 P population (ISS Figure 4.1-1A). The median time to onset of LVEF below 50% and/or absolute decrease of 10% or more from baseline in patients who met the criteria occurred slightly earlier at 0.8 and 1.0 months in Study CMEK162A2301 and the all melanoma Bini 45 P population, respectively (ISS Figure 4.1-2A).

In the Combo 450 ISP, Grade ≥3 left ventricular dysfunction events developed in 1.3% (5/372) of patients; of them, 2 patients (2.0%) in the NSCLC population and 3 patients (1.1%) in the Combo 450 RP (Melanoma population), while in the Combo 450 arm of Study CMEK162B2301 Grade ≥3 events developped in 1.6% (3/192) of patients. The majority of events in the Combo 450 arm of Study CMEK162B2301 was Grade 2 (4.2%).

In the Combo 450 ISP, the median time to first onset of left ventricular dysfunction was 5.2 months [range 0.0-25.7 months].

In the Combo 450 RP population (Melanoma population), the median time to first onset of left ventricular dysfunction was 4.4 months [range 0.0-21.3 months]. In the NSCLC population, the median time to first onset was 6.9 months [range 0.9-25.7 months].

in the Combo 450 ISP, few patients discontinued Combo 450 mg due to left ventricular dysfunction (0.8%), 6.2% patients required dose adjustment or study drug interruption and 1.9% required additional therapy.

Outcome:

Table SVII.3: Adverse event outcome for left ventricular dysfunction (CMEK162A2301)

		Melanoma
PT	**Outcome status**	**Binimetinib 45 mg BID N=269* n (%)**
Ejection fraction decreased overall	Recovered/Resolved	20/33 (60.6)
	Recovering/Resolving	1/33 (3.0)
	Unknown/Missing	4/33 (12.1)
	Not Recovered/Not resolved	8/33 (24.2)
Ejection fraction abnormal overall	Not Recovered/Not resolved	1/1 (100.0)
Left ventricular dysfunction overall	Recovered/Resolved	2/2 (100.0)

Sources: ISS supp: Table 2.6.8.2a.
Melanoma: Naive to BRAF inhibitors and MEK inhibitors. A patient is counted once within each PT and ADR grouping.
For each patient, the last collected status of the outcome by PT is considered. The worst-case scenario was taken when there were 2 outcomes at the same date for the same PT, ranging: 'Fatal', 'Ongoing', 'Not Recovered/Not Resolved', 'Unknown/Missing', 'Recovering/Resolving', 'Recovered/Resolved with Sequelae', 'Resolved'.
Ongoing outcomes represent the 'Not Recovered/Not Resolved' outcomes at the study cut-off date.
*The study CMEK162X2201 was excluded because the outcome status was not collected.

In the Combo 450 ISP, the left ventricular dysfunction was reversible in the majority of patients as the outcome of left ventricular dysfunction events was recovered/resolved in 25 of the 35 patients (71.4%) with the event. For the most frequently reported PT ejection fraction decreased, the outcome was recovered/resolved in the majority (71.4%; 20/28) of patients.

In the Combo 450 arm of Study CMEK162B2301, for the most frequently reported PT i.e. ejection fraction decreased, for 88.2% (15/17) of patients an outcome of resolved was reported. The majority of patients with left ventricular dysfunction were managed with dose interruption or dose reduction and the event was reversible in the majority of patients.

Reversibility:

In the absence of specific consensus guidelines on the management of left ventricular dysfunction arising from MEK inhibitor treatment in metastatic melanoma patients, left ventricular dysfunction should be managed per local guidelines. Previous publications have recommended that patients be closely monitored for the entire duration of treatment (Mascarucci 2016).

If a reduction in LVEF is found, the condition can typically be managed by reducing or stopping the MEK inhibitor dependent on the severity of the symptoms (Welsh 2015). Those with Grade 1 (absolute decrease in LVEF <10% from baseline) or Grade 2 (absolute ≥10% to <20% decrease in LVEF from baseline) symptoms may have their BRAF and/or MEK inhibitor withheld for up to four weeks. If improved to near normal, the BRAF and/or MEK inhibitor may be resumed at a lower dosage level (Welsh 2015). Welsh *et al*. recommend that for Grade 1 or 2 patients who do not show improvement to normal after at least two dose reductions, permanent discontinuation of the BRAF

and/or MEK inhibitor may be considered (Welsh 2015). If LVEF reduction results in Grade 3 or 4 poorly controlled or refractory heart failure, MEK inhibitor treatment should be discontinued and symptoms treated, and the symptoms investigated via a standard cardiac workup, including ECG, ECHO, and referral to a cardiologist (Welsh 2015).

Long-term outcomes

The impact of the risk of left ventricular dysfunction on the individual patient will depend on the severity and duration of the symptoms experienced. Modification or dose discontinuation of other BRAF inhibitors such as vemurafenib can result in the resolution of the cardiotoxicity (Mascarucci 2016); therefore, similar dose modifications of binimetinib, combined with supportive therapy and proper monitoring for the entire duration of the treatment, are expected to result in a lower risk of adverse long-term outcomes.

Impact on quality of life

It is possible to have asymptomatic reductions in LVEF which would be expected to have no impact on patient quality of life, though impact to the patient is dependent on the duration and severity of symptoms experienced. Those with serious left ventricular dysfunction experiencing symptomatic heart failure may have severe impacts on their quality of life, as serious reductions in LVEF may require treatment with a ventricular assist device, intravenous vasopressor support or heart transplantation. However, with proper monitoring, timely detection and intervention, and the correct management according to local standards of care, including dose modification and treatment discontinuation, cardiotoxicity is expected to be transient. Therefore, minimal impact on a patient's quality of life can be expected in the long-term.

Risk factors and risk groups:

Patients with significant heart problems were excluded from the binimetinib clinical trials.

Among the patients who were included in the binimetinib clinical studies, no risk groups or factors have been identified. LVEF shift data were assessed in patients with or without baseline cardiac risk factors (defined as current/ex-smoker and/or history of hypertension, diabetes, hyperlipidaemia cardiac disorders, arteriosclerosis and ischemic heart disease) with most patients having baseline risk factors. These data showed no difference in the percent of patients LVEF shifts for patients with worst post-baseline LVEF by baseline cardiac risk factor category 'yes' or 'no'.

Myocardial dysfunction is modified by genetic factors and impaired myocardial function before initiating cancer treatment, arterial hypertension, >65 years of age, body mass index >30 kg/m2 and radiotherapy increase the risk. The onset of left ventricular dysfunction after application of MEKi or BRAFi+MEKi therapy ranges from 2 weeks to 5 months and 1–13 months, respectively, and resolved in the majority of cases (Shah 2015, Heinzerling 2019).

Preventability:

This risk may be prevented through physician awareness, patient information, routine monitoring of LVEF and early identification of signs and symptoms. Echography or MUGA at baseline and regularly during treatment will allow appropriate management. Please see PART V for further details.

Impact on the benefit-risk balance of the product:

The risk of left ventricular dysfunction should be satisfactorily minimised through the routine risk minimisation measures described in PART V.

Public health impact (Expected population outcome):

EUCAN data from 2012 indicate an age standardised incidence rate of malignant melanoma of the skin in the EU of 13.0 per 100,000 of population per year (European Cancer Information System*).* There are currently 508 million individuals living in the EU (European Commission). Assuming that 20% of diagnosed melanomas progress to a metastatic stage, and that approximately 50% of these cases are positive for BRAF V600E mutations (Ascierto 2012), the target population is estimated to be approximately 6,552 individuals per year.

Given the absolute risk of left ventricular dysfunction events described above for patients treated with binimetinib alone (0.103), an estimate of the 675 patients receiving this therapeutic regimen may be expected to develop left ventricular dysfunction events in a population of 6,552 eligible patients each year.

Given the absolute risk of decreased ejection fraction (PT) described above for patients treated with binimetinib alone (0.094), an estimated 616 patients receiving this therapeutic regimen may be expected to develop decreased ejection fraction in a population of 6,552 eligible patients each year.

Given the absolute risk of cardiac ventricular dysfunction events, described above for patients treated with binimetinib, and encorafenib (0.084), it can be estimated that 794 of the patients receiving this therapeutic regimen may be expected to develop LVD events in a population of 9,460 eligible patients each year.

In Europe, using the estimated value of 477,500 new cases of lung cancer diagnosed in 2020 (Dyba, 2021), and assuming that about 80% of newly diagnosed lung cancers are NSCLC (American Cancer Society, 2021), with 60% of NSCLC patients are diagnosed at advanced stage (stages IIIB/C and IV), and approximately 3% of them are positive for BRAF V600 mutations with 50% of them driven by the BRAF V600E mutation (Class 1), it can be estimated that approximately 3,438 individuals presented with BRAF V600E-mutated advanced lung cancer in 2020 across EU countries.

Given the absolute risk of left ventricular dysfunction events described above for patients treated with binimetinib alone (0.103), an estimated 354 patients receiving this therapeutic regimen, may be expected to develop left ventricular dysfunction events in a population of 3,438 eligible patients each year if they are all treated.

Given the absolute risk of cardiac ventricular dysfunction events, described above for patients treated with binimetinib and encorafenib (0.084), it can be estimated that 289 of the patients receiving this therapeutic regimen may be expected to develop LVD events in a population of 3,438 eligible patients each year.

It is to be noted however, that safety data from clinical trials may not be necessarily extrapolated to the real-world target population, as patients enrolled in clinical trials from a specific, controlled subset of patients fulfilling strict inclusion criteria, without severe comorbidities and certain concomitant medications.

(ii) Important identified risk: Haemorrhage

Potential mechanisms:

Not identified.

A review of the literature showed that the mechanism of haemorrhage with a MEK or BRAF inhibitor is currently unknown. In one case, a rapid tumour response to treatment with the MEK and BRAF inhibitor combination trametinib and dabrafenib, reportedly resulted in a hepatic haemorrhage, the tumour necrosis in solid organs or near vital structures having rapidly changed the anatomic environment (Flaherty 2015). However, this aetiology cannot explain most cases of haemorrhages seen with MEK or BRAF inhibitors.

Based on another publication, the mechanism behind a case of intracranial haemorrhage caused by combined dabrafenib and trametinib therapy is still unclear (Lee 2014). Dabrafenib which has greater penetration into the brain than vemurafenib, has demonstrated activity in melanoma which is metastatic to the brain; additional factors which may play a role are prior brain surgery and/or radiation therapy.

Evidence source and strength of evidence:

Haemorrhage is a known class effect of MEK inhibitors as a single-agent or in combination (*Cotellic® [cobimetinib] SmPC, Mekinist® [trametinib] SmPC*) and is considered as an important identified risk for binimetinib.

ADRs in the grouped term of haemorrhage were reported as common for binimetinib. There is sufficient scientific evidence to suspect a causal association between binimetinib and this risk.

Characterisation of the risk:

Frequency with 95% CI:

In melanoma patients in the Bini 45 P population (N=427), haemorrhage events (based on AESI grouping) were reported in 13.6% of patients. In Study CMEK162A2301, haemorrhage events were reported in 12.3% of patients in the binimetinib arm.

In melanoma patients in the Bini 45 P population (N=427), the most frequently reported PTs were epistaxis (13 (3.0%) patients) and retinal haemorrhage (7 (1.6%) patients). In the binimetinib arm in Study CMEK162A2301, the most frequently reported PTs were epistaxis (9 (3.3%) patients) and retinal haemorrhage (6 (2.2%) patients) (Table RMP2.1-9, Table RMP2.2-9).

Table SVII.4: Summary of haemorrhage events (Bini 45 P)

Haemorrhage Events	**All Melanoma Bini 45 P N=427 n (%)**
Overall incidence	49 (11.5)
Related overall incidence	15 (3.5)
Grade 3 to 4	10 (2.3)
PT with incidence >10%	None
SAEs overall incidence	10 (2.3)
AEs leading to discontinuation	3 (0.7)
AEs leading to dose change/reduction/interruption	5 (1.2)
AEs requiring additional therapy	5 (1.2)

Sources: ISS-PART 1_U Table 2.1.19.1-u, Table 2.1.19.2-u and Table 2.1.19.3-u.
A patient with multiple occurrences is counted only once with the maximum reported severity.
MedDRA Version 19.0 and (Compound Case Retrieval Strategy_Binimetinib_MedDRA 18.1_09Nov2015) have been used for the reporting of adverse events.
Events included (PTs): Anal haemorrhage, blood urine, contusion, diarrhoea haemorrhagic, epistaxis, gastric haemorrhage, genital haemorrhage, gingival bleeding, haematemesis, haematochezia, haematoma, haematuria, haemoptysis, haemorrhage, haemorrhage intracranial, haemorrhoidal haemorrhage, optic nerve sheath haemorrhage, petechiae, pulmonary haemorrhage, rectal haemorrhage, retinal haemorrhage, scrotal haematoma, skin haemorrhage, subarachnoid haemorrhage, subdural haematoma, tumour haemorrhage, vaginal haemorrhage.

Overall haemorrhagic events occurred at a frequency of 16.7%, 16.7% respectively in the Combo broad ISP population and the Combo 450 ISP. In the Combo 450 RP (Melanoma population), haemorrhagic events occurred at a frequency of 17.9% (19.3% in the Combo 450 arm of study CMEK162B2301). In the NSCLC population, haemorrhagic events occurred at a frequency of 13.3%.

Haemorrhage incorporated a wide spectrum of PTs, most of them with a single event, most of them indicative of minor haemorrhage.

In the Combo 450 ISP, haemorrhagic events included haematuria and haematochezia in 2.7% (10/372) of patients each, rectal haemorrhage in 2.2% (8/372) of patients, retinal haemorrhage in 1.3% (5/372) of patients, and cerebral haemorrhage, anal haemorrhage and conjunctival haemorrhage in 1.1% (4/372) of patients, each. Remaining PTs occurred in < 1% of patients. Grade ≥ 3 occurred in 3.5% (13/372) of patients. Drug discontinuation required due to haemorrhage in 0.8% (3/372) of patients, 2.4% required dose adjustment or study drug interruption and 5.1% required additional therapy.

In the Combo 450 RP population (Melanoma population), haemorrhagic events included haematuria in 3.3% (9/274) of patients, rectal haemorrhage and haematochezia in 2.9% (8/274) of patients each, retinal haemorrhage in 1.8% (5/274) of patients, cerebral haemorrhage and conjunctival haemorrhage in 1.5 (4/274) of patients, each, and intermenstrual bleeding in 1.1% (3/274) patients. Other PTs occurred in <1% of patients. Grade ≥3 occurred in 3.3% of patients, 1.1% patients discontinued Combo 450 due to haemorrhage, 1.5% required dose adjustment or study drug interruption and 4.7% required additional therapy.

In the NSCLC population, haemorrhagic events included anal haemorrhage in 3.1% (3/98) of patients, haematochezia, haemothorax and haemoptysis in 2.0% (2/98) of patients, each. Remaining PTs occurred in ≤1% of patients. Grade ≥3 occurred in 4.1% (4/98) of patients. No drug discontinuation was required due to haemorrhage. Additional therapy was required in 6 patients (6.1%), and dose adjustment or study drug interruption was required in 5 patients (5.1%).

Table SVII.5: Binimetinib and encorafenib combination: Summary of haemorrhage events

	Combo 450 ISP	**NSCLC population**	**Combo broad ISP**	**Melanoma population**	**Study CMEK162B2301**
Haemorrhage	**Combo 450mg QD N=372 n (%)**	**Combo 450mg QD N=98 n (%)**	**Combo ISP BP N=531 n (%)**	**Combo 450 RP N=274 n (%)**	**Combo 450mg QD N=192 n (%)**
Overall incidence	62 (16.7)	13 (13.3)	89 (16.7)	49 (17.9)	37 (19.3)
Related overall incidence	11 (3.0)	2 (2.0)	16 (3.0)	9 (3.3)	8 (4.2)
Grade 3+	13 (3.5)	4 (4.1)	22 (4.1)	9 (3.3)	7 (3.6)
PT with incidence > 10%	none	none	none	none	none
SAEs overall incidence	15 (4.0)	6 (6.1)	25 (4.7)	9 (3.3)	7 (3.6)
% discontinuation	3 (0.8)	0	5 (0.9)	3 (1.1)	3 (1.6)
% dose change/reduction	9 (2.4)	5 (5.1)	15 (2.8)	4 (1.5)	3 (1.6)
% additional therapy	19 (5.1)	6 (6.1)	28 (5.2)	13 (4.7)	11 (5.7)
EAIR (PT) [1]	1.34	1.06	1.48	1.44	1.51

Sources: Table 2.1.19.1-u, Table 2.1.19.2-u and Table 2.1.19.3-u
Sources: W00090_NSCLC – Version date: 25JUL2023 12:20 – File Name: Sub5_3_4_c1_RMPHaemoEnBi_saf_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 – Dataset ADSP1.ADADR:24JUL2023 ADSP1.ADSL:27JUN2023 – PGM Sub5_3_4_c1_RMPHaemoEnBi_saf_t.sas 30JUN2023 12:29
[1] EAIR (Exposure adjusted incidence rate per 100 patient-months) = (n*100)/total exposure time (in months) of Safety Set
MedDRA Version 25.1 has been used for the reporting of adverse events.

Kaplan Meier plots of time to first grade ≥2 haemorrhage for patients with an event showed a median time to onset of 4.8 months (95% CI: 0.5, 10) in the Combo 450 arm of study CMEK162B2301.

Haemorrhagic events at various sites and mostly mild in severity were very commonly reported in patients receiving the combination therapy. The incidence rates were numerically higher in the combination population as compared to binimetinib single agents.

Haemorrhage is identified as an ADR for binimetinib single agent and for the combination of binimetinib and encorafenib. In the Combo 450 ISP, the reason for the higher overall incidence of haemorrhagic events is unclear, possibly due to the longer median duration of exposure in the Combo 450 ISP or other alternate factors to be investigated.

KM plots of time to first grade ≥2 Haemorrhage for patients with an event showed a relatively similar median time to onset for the Bini P population (2.8 months; 95% CI: 0.4, 4.1) and the Combo 450 ISP (2.8 months; 95% CI: 0.5, 6.1).

In the post-marketing experience, cumulatively up to 26 June 2023 (DLP of the most recent PSUR), 201 cases were identified in the global safety database (representing 3.9% of all post-marketing cases) reporting 226 events indicative for haemorrhage. Of them, 184 were serious. The PTs most frequently reported included haematochezia (23 events), gastrointestinal haemorrhage (21 events), rectal haemorrhage (18 events), haemorrhage, melaena (13 events each), cerebral haemorrhage, haematuria (9 events each), contusion (8 events), epistaxis (6 events), intestinal haemorrhage, intracranial tumour haemorrhage, lower gastrointestinal haemorrhage, and upper gastrointestinal haemorrhage (5 events each). These cases concerned 102 females, 92 males while the gender was not reported in 7 cases, the mean patients' age was 63.8 years.

Absolute risks

The absolute risk of haemorrhage events was 0.115 in the Bini 45 P and 0.023 for severe haemorrhage events (Grade 3/4) in the Bini 45 P.

The absolute risk of haemorrhage events in the Combo 450 RP (Melanoma population) was 0.172.

The absolute risk of Grade 3/4 haemorrhage events in the Combo 450 RP (Melanoma population) was 0.033.

Relative risks as compared with "unexposed" patient populations

In order to perform the RR calculations, a literature search was undertaken to identify European studies reporting the risk of haemorrhage in real-world, BRAF-mutated metastatic melanoma patients who were unexposed to binimetinib single agent, or to any interventions in the same therapeutic class (i.e. any MEK inhibitor for binimetinib single agent).

No studies reporting the risk of haemorrhage in a relevant "unexposed" patient population were identified for the purposes of the binimetinib single agent RR calculations; therefore, no RR calculations could be performed.

In order to perform the RR calculations, a literature search was undertaken to identify European studies reporting the risk of haemorrhage in real-world, BRAF-mutated metastatic NSCLC patients who were unexposed to binimetinib single agent, or to any interventions in the same therapeutic class (i.e. any MEK inhibitor for binimetinib single agent).

No studies reporting the risk of LVD in a relevant "unexposed" patient population were identified for the purposes of the binimetinib single agent RR calculations; therefore, no RR calculations could be performed.

Seriousness:

In melanoma patients in the Bini 45 P population (N=427), SAEs of haemorrhage (based on AESI grouping) were reported in 10 (2.3%) patients (PTs of pulmonary haemorrhage [2 (0.5%) patients], and diarrhoea haemorrhagic, haematoma, haemoptysis, haemorrhage, haemorrhage intracranial, skin haemorrhage, subarachnoid haemorrhage, subdural haematoma, and tumour haemorrhage [1 (0.2%) patient each]).

In the binimetinib arm of Study CMEK162A2301, SAEs of haemorrhage events were reported for 6 (2.2%) patients (PTs of haemoptysis, haemorrhage, haemorrhage intracranial, skin haemorrhage, subarachnoid haemorrhage, subdural haematoma, and tumour haemorrhage [1 (0.4%) patient each]) (Table RMP2.1-9 and Table RMP2.2-9).

In Study CMEK162A2301, a binimetinib-treated patient was reported to have had a fatal haemorrhage event. The patient with malignant melanoma in the right temporal region, and neck, lung and pancreatic metastases. He experienced bleeding on the right side of the neck

(haemorrhage, Grade 4), with ulceration. The patient died 4 days later due to disease progression, respiratory arrest and haemorrhage, which were considered as not related to binimetinib. Binimetinib was ongoing at the time of death.

In the Combo 450 ISP, serious haemorrhage events were reported in 4.0% (15/372) of patients:

In the Combo 450 RP population (Melanoma population), serious haemorrhage events were reported in 3.3% (9/274) of patients including 3.6% (7/192) of patients in the Combo 450 arm of Study CMEK162B2301. In the NSCLC population, serious haemorrhage events were reported in 6.1% (6/98) of patients.

Fatal gastric ulcer haemorrhage with multiple organ failure as a concurrent cause of death, occurred in one patient in Melanoma population. Cerebral haemorrhage/ haemorrhage intracranial occurred in 1.3% (5/372) of patients in the Combo 450 ISP, with fatal outcome in 4 patients. The PT: Cerebral haemorrhage occurred in 1.5 % (4/274) of patients with fatal outcome in 3 patients in the Combo 450 RP population (Melanoma population), and PT: haemorrhage intracranial (with fatal outcome) occurred in one patient (1/98; 1.0%) in the NSCLC population (this event was assessed as treatment-related by the Investigator, however, considered as not related to study treatment by the Sponsor). All events occurred in the setting of new or progressive brain metastases.

Severity:

In melanoma patients in the Bini 45 P population, Grade 3/4 AEs in the haemorrhage events were reported for 10 (2.3%) and 5 (1.9%) patients in the all melanoma Bini 45 P population and in the binimetinib arm of Study CMEK162A2301, respectively (Table RMP2.1-9). Haemorrhage events led to discontinuation of binimetinib in 3 (0.7%) patients and to dose interruption or adjustment in 5 (1.2%) patients.

For patients with an event, Kaplan-Meier plots of time to first Grade ≥2 haemorrhage event showed a median time to onset of 1.2 months for patients in the binimetinib arm of Study CMEK162A2301 and 2.4 months for patients in the all melanoma Bini 45 P population (ISS Figure 2.1-9A).

KM plots of time to first grade ≥2 Haemorrhage for patients with an event showed a median time to onset in the Combo 450 ISP population of 2.8 months.

Grade ≥ 3 haemorrhage events were reported in 3.5% (13/372) of patients in the Combo 450 ISP (3.3% (9/274) of patients in the Combo 450 RP [Melanoma population]; in 3.6% (7/192) of patients in the Combo 450 arm of Study CMEK162B2301, and 4.1% (4/98) of patients in the NSCLC population).

A limited number of events required additional therapy (5.1% of the Combo 450 ISP, including 4.7% in the Combo 450 RP [Melanoma population]; 5.7% in the Combo 450 arm of Study CMEK162B2301, and 6.1% in the NSCLC population). Few events led to study drug discontinuation (0.8% in the Combo 450 ISP, including 1.1% in the Combo 450 RP [Melanoma population]; 1,6% in the Combo 450 arm of Study CMEK162B2301, and none in the NSCLC population), or required dose adjustment/study drug interruption (2.4% in the Combo 450 ISP, including 1.5% in the Combo 450 RP [Melanoma population]; 1.6% in the Combo 450 arm of Study CMEK162B2301, and 5.1% in the NSCLC population).

Outcome:

Table SVII.6: Adverse event outcome status for haemorrhage (CMEK162A2301)

		Melanoma
PT	**Outcome status**	**Binimetinib 45 mg BID N=269* n (%)**
Anal haemorrhage overall	Recovering/Resolving	1/1 (100.0)
Epistaxis overall	Recovered/Resolved	8/9 (88.9)
	Not Recovered/Not resolved	1/9 (11.1)

		Melanoma
PT	**Outcome status**	**Binimetinib 45 mg BID N=269* n (%)**
Haematochezia overall	Recovered/Resolved	1/1 (100.0)
Haematuria overall	Recovered/Resolved	1/2 (50.0)
	Recovering/Resolving	1/2 (50.0)
Haemoptysis overall	Recovered/Resolved	2/2 (100.0)
Haemorrhage overall	Fatal	1/1 (100.0)
Haemorrhoidal haemorrhage overall	Recovered/Resolved	1/2 (50.0)
	Not Recovered/Not resolved	1/2 (50.0)
Retinal haemorrhage overall	Recovered/Resolved	3/6 (50.0)
	Not Recovered/Not resolved	3/6 (50.0)
Subdural haematoma overall	Recovered/Resolved	1/1 (100.0)
Tumour haemorrhage overall	Recovering/Resolving	1/1 (100.0)
Vaginal haemorrhage overall	Recovered/Resolved	1/1 (100.0)

Sources: ISS Supp: Table 2.6.8.2a.
Melanoma: Naive to BRAF inhibitors and MEK inhibitors. A patient is counted once within each PT and ADR grouping.
For each patient, the last collected status of the outcome by PT is considered. The worst-case scenario was taken when there were 2 outcomes at the same date for the same PT, ranging: 'Fatal', 'Ongoing', 'Not Recovered/Not Resolved', 'Unknown/Missing', 'Recovering/Resolving', 'Recovered/Resolved with Sequelae', 'Resolved'.
Ongoing outcomes represent the 'Not Recovered/Not Resolved' outcomes at the study cut-off date.
*The study CMEK162X2201 was excluded because the outcome status was not collected.

In the Combo 450 ISP, five events with fatal outcomes were reported: 3 cerebral haemorrhage (related to tumour progression and haemorrhage into tumour metastases), one gastric ulcer haemorrhage, considered not related to Combo 450 mg; these events were reported in the Combo 450 RP (Melanoma population), and haemorrhage intracranial which was reported in the NSCLC population and assessed as treatment-related by the investigator.

Table SVII.7: Binimetinib and encorafenib combination: Adverse event outcome for most common haemorrhage events

PT*	**Outcome status [1]**	**Combo 450 ISP** N=372 n (%)**	**Study CMEK162B2301 Combo 450mg QD N=192 n (%)**
Gastrointestinal haemorrhage events			
Rectal haemorrhage	Recovered/Resolved	6/8 (75.0)	6/8 (75.0)
	Not Recovered/Not resolved	2/8 (25.0)	2/8 (25.0)
Haematochezia	Recovered/Resolved	7/10 (70.0)	4/6 (66.7)
	Recovering/Resolving	1/10 (10.0)	1/6 (16.7)
	Not Recovered/Not resolved	2/10 (20.0)	1/6 (16.7)
Other			
Haematuria	Recovered/Resolved	8/10 (80.0)	3/5 (60.0)
	Not Recovered/Not resolved	1/10 (10.0)	1/5 (20.0)
	Unknown/Missing	1/10 (10.0)	1/5 (20.0)

Sources: ISS Part1_u. Table 2.6.8.a
Sources: W00090_NSCLC - Version date: 25JUL2023 12:15 - File Name: Sub5_1_6_c1_RMPAdrOutSum_treat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADADR:24JUL2023 ADSP1.ADSL:27JUN2023 - PGM Sub5_1_6_c1_RMPAdrOutSum_treat_t.sas 04MAY2023 11:16
** haemorrhage events occurred in ⩾2.0%*
*** N represents the number of patients in the considered PT, a patient is counted once by PT.*
[1] For each patient, the last collected status of the outcome by PT is considered.
The worst case scenario was taken when there were 2 outcomes at the same date for the same PT
MedDRA Version 25.1 was used for the reporting of adverse events.

Reversibility

In the absence of specific consensus guidelines on the management of haemorrhagic events arising from MEK inhibitor treatment in metastatic melanoma patients, haemorrhage should be managed per local guidelines (Welsh 2015). Haemorrhage treatment is likely to vary with the severity and location of the bleeding. Furthermore, treatment of visible bleeding in patients with cancer must be individualised and include general resuscitative measures (i.e. volume and fluid replacement) and specific measures to stop the haemorrhage (Pereira 2004). Local interventions may include packing, haemostatic agents and dressings, radiotherapy, endoscopic treatments, transcutaneous arterial embolisation and surgery. Systemic medical interventions can also be used, including blood products for replacement (Pereira 2004).

A case report of a patient using dabrafenib and trametinib for metastatic melanoma experienced an intracranial haemorrhage that was promptly managed with a craniotomy. The patient regained full neurological function post-operatively, suggesting that if the proper treatment and care is received in a timely manner, even significant haemorrhages can be reversible (Lee Le 2014).

Long-term outcomes

While long-term results are not available at this time, the impact of the risk of haemorrhage on the individual patient is highly dependent on the severity of the haemorrhage. If identified early, and well controlled with local or systemic therapy, recovery may be expected. In cases of diffuse or severe haemorrhage that do not respond to supportive treatment, it is possible that long-term outcomes may include death, especially for patients with intra-tumoural haemorrhage within brain metastases (Ly 2015).

Impact on quality of life

The impact on quality of life of haemorrhage can be expected to depend on the severity and location of the haemorrhage. Minor haemorrhage is usually acute and therefore likely to have a minimal impact on quality of life if treated successfully, particularly for longer-term effects. However, a major or sub-optimally managed haemorrhage could result in a severe impact on a patient's quality of life.

Risk factors and risk groups:

Patients receiving antiplatelet and anticoagulant medications in combination with any other treatment which may cause bleeding are at greater risk of haemorrhage.

Preventability:

Bleeding events are routinely monitored in cancer treated patients.

This risk may be prevented through physician awareness, patient information, treatment of modifiable risk factors and early identification of signs and symptoms. Please see PART V for further details.

Patient information is important for early reporting of symptoms of bleeding events to prevent complications. Anti-coagulant or anti-platelet treatment should be balanced with the risk of haemorrhage, based on individual patient characteristics and risk factors.

Impact on the benefit-risk balance of the product:

Haemorrhage is an important identified risk for the combination. Cases occurred at a mean incidence of 16.7%. Grade ≥3 events were reported in 4.1%, 3.5% and 3.6% of patients for the Combo broad ISP population, the Combo 450 ISP population, and the Combo 450 arm of study CMEK162B2301 respectively.

Based on the available data, the identified risk of haemorrhage of the combination binimetinib and encorafenib does not outweigh the potential benefit to patients, given the target population, and is satisfactorily minimised through the routine risk minimisation measures described in Part V.

Public health impact (Expected population outcome):

EUCAN data from 2012 indicate an age standardised incidence rate of malignant melanoma of the skin in the EU of 13.0 per 100,000 of population per year (European Cancer Information System*).* There are currently 508 million individuals living in the EU (European Commission). Assuming that 20% of diagnosed melanomas progress to a metastatic stage, and that approximately 50% of these cases are positive for BRAF V600E mutations (Ascierto 2012), the target population is estimated to be approximately 6,552 individuals per year.

Given the absolute risk of haemorrhage described above for patients treated with binimetinib alone (0.115), an estimated 753 patients receiving this therapeutic regimen may be expected to develop haemorrhage events in a population of 6,552 eligible patients each year if all are treated.

Given the absolute risk of severe haemorrhagic events (Grade 3/4) described above for patients in the Bini 45 P population (0.023), an estimated 151 patients receiving this therapeutic regimen may be expected to develop severe haemorrhage events in a population of 6,552 eligible patients each year if all are treated.

In Europe, using the estimated value of 477,500 new cases of lung cancer diagnosed in 2020 (Dyba, 2021), and assuming that about 80% of newly diagnosed lung cancers are NSCLC (American Cancer Society, 2021), with 60% of NSCLC patients are diagnosed at advanced stage (stages IIIB/C and IV), and approximately 3% of them are positive for BRAF mutations with 50% of them driven by the BRAF V600E mutation (Class 1), it can be estimated that approximately 3,438 individuals presented with BRAF V600E-mutated advanced lung cancer in 2020 across EU countries.

Given the absolute risk of haemorrhage described above for patients treated with binimetinib alone (0.115), an estimated 395 patients receiving this therapeutic regimen may be expected to develop haemorrhage events in a population of 3,438 eligible patients each year if all are treated.

Given the absolute risk of severe haemorrhagic events (Grade 3/4) described above for patients in the Bini 45 P population (0.023), an estimated 79 patients receiving this therapeutic regimen may be expected to develop severe haemorrhage events in a population of 3,438 eligible patients each year if all are treated.

It is to be noted however, that safety data from clinical trials may not be necessarily extrapolated to the real-world target population, as patients enrolled in clinical trials from a specific, controlled subset of patients fulfilling strict inclusion criteria, without severe comorbidities and certain concomitant medications.

(iii) Important identified risk: Hepatotoxicity

Potential mechanisms:

Hepatic adverse reactions are identified as primarily binimetinib-driven in the combination.

Slight increases in hepatic transaminase values were seen in rats and monkeys receiving binimetinib, however, no mechanism has been identified. Hepatic lesions have not been identified in non-clinical studies. The elevation of hepatic enzymes tended to normalise with continued treatment. Hepatotoxicity has been observed with various TKIs with different chemical structure. A chemical class effect based on inhibition of a specific tyrosine kinase is unlikely because pharmacologically diverse TKIs are known to be hepatotoxic (Shah 2013).

The pattern of hepatotoxicity is predominantly idiosyncratic. Pharmacogenomics show potential in predicting patients at risk of poorly metabolising or developing immune-allergic responses to molecular targeted agents, but prospective data is scant (Lee 2016). For binimetinib, or the combination binimetinib and encorafenib, the potential mechanism is unknown.

Evidence source and strength of evidence:

Liver laboratory abnormalities represent a class-effect risk for both MEK inhibitors and BRAF inhibitors, as single-agents or in combination *(Zelboraf® [vemurafenib] SmPC, Tafinlar® [dabrafenib]*

SmPC, Cotellic® [cobimetinib] SmPC, Mekinist® [trametinib] SmPC), and hepatotoxicity is considered an important identified risk for the combination encorafenib and binimetinib. Increased ALT, AST and GGT are identified as ADRs for the combination.

Characterisation of the risk:

Frequency with 95% CI:

In melanoma patients in the Bini 45 P population (N=427), overall liver events were reported in 17.3% of patients. In Study CMEK162A2301, liver events were reported in 19.0% of patients in the binimetinib arm.

In melanoma patients in the Bini 45 P population (N=427), the most frequently reported PTs were AST increased (13.8%) and ALT increased (9.6%); no other PTs were reported at ≥5.0% incidence. In the binimetinib arm in Study CMEK162A2301, the most frequently reported PTs were AST increased (13.4%) and ALT increased (8.2%) (Table RMP2.2-14).

The frequency of reporting of AST increased should be regarded in the context of muscle toxicities, as AST is not liver-specific.

In the Combo 450 ISP, transaminases increased (PTs: ALT increased, AST increased, transaminases increased, hepatic enzyme increased and hypertransaminasaemia) occurred in 16.4% of patients (ALT 13.2% and AST 11.0%), including 6.5% of patients with grade ≥ 3 events. Combo 450 was discontinued in 1.3% of patients in the Combo 450 ISP due to transaminases increased, 6.7% required dose adjustment or study drug interruption and 1.3% required additional therapy. The median time to first onset of transaminases increased was 1.0 months; range 0.0-23.8 months.

In the Combo 450 RP (Melanoma population), transaminases increased events occurred in 16.1% of patients (ALT 13.1% and AST 9.5%), including 5.5% of patients with grade ≥ 3 events. In addition, 1.8% discontinued Combo 450 due to transaminases increased, 6.2% required dose adjustment or study drug interruption and 1.5% required additional therapy. The median time to first onset of transaminases increased was 1.0 month (range 0.0-17.5 months). A similar incidence of transaminases increased was seen in the Combo 450 arm of study CMEK162B2301, occurring in 13.5% of patients, and the median time to first onset of transaminases increase was 30 days (range 1-534 days).

In the NSCLC population, transaminases increased events occurred in 17.3% of patients (ALT 13.3% and AST 15.3%), including 9.2% of patients with grade ≥ 3 events. No patient required discontinuation of Combo 450 due to transaminases increased. Dose adjustment or study drug interruption was required in 8.2% of patients, and additional therapy required in one patients (1.0% of patients). The median time to first onset of transaminases increased was 1.4 months (range 0.0-23.8 months).

In the Combo 450 ISP, increased ALT >3 x upper limit of normal (ULN) were reported in 11.4%, and increased ALT or AST>3 x ULN were reported in 12.8% of patients (10.1% and 11.7% of patients respectively in the Combo 450 RP (Melanoma population), and 15.1% and 16.1% in the NSCLC population, respectively).

In the Combo 450 ISP population, GGT increased was reported in 11.3% of patients (14.6% of patients in Combo 450 RP [Melanoma population] and 2.0% of patients in the NSCLC population), 6.7% of patients had grade ≥ 3 events (8.4% of patients in Combo 450 RP [Melanoma population] and 2.0% in the NSCLC population). No serious cases were reported, 0.5% discontinued due to GGT increased, 2.7% required dose adjustment or study drug interruption and 0.3% required additional therapy. There were no cases meeting the case-finding criteria of Hy's law in the Combo 450 ISP.

Blood bilirubin increased was reported in only 3 patients (0.8%) in the Combo 450 ISP (2 patients in the Combo 450 arm of study CMEK162B2301 and 1 patient in the NSCLC population). None of them was serious.

In the Combo 450 RP (Melanoma population), one hepatic failure event (PT: hepatic failure*)* was reported in 1 patient (patient from the Combo 450 arm of Study CMEK162B2301). It occurred

8.7 months after study combination initiation and was considered unrelated to study drugs and due to the underlying extensive metastatic liver disease. No hepatic failure was reported in the NSCLC population.

Table SVII.8: Summary of overall liver events (Bini 45 P and binimetinib in combination with encorafenib)

Liver events						
Liver function test	**Combo 450 ISP Combo 450mg QD N=372 n (%)**	**NSCLC population Combo 450mg QD N=98 n (%)**	**All Melanoma Bini 45 P N=427 n (%)**	**Combo broad ISP (Combo ISP BP) N=531 n (%)**	**Melanoma population (Combo 450 RP) N=274 n (%)**	**Study CMEK162B2301 Combo 450mg QD N=192 n (%)**
Overall incidence	89 (23.9)	18 (18.4)	74 (17.3)	128 (24.1)	71 (25.9)	47 (24.5)
Related overall incidence	67 (18.0)	14 (14.3)	60 (14.1)	102 (19.2)	53 (19.3)	35 (18.2)
Grade 3+	44 (11.8)	10 (10.2)	18 (4.2)	61 (11.4)	34 (12.4)	27 (14.1)
PT with incidence ⩾ 5% [1]						
GGT increased*	42 (11.3)	2 (2.0)	15 (3.5)	48(9.0)	40 (14.6)	29 (15.1)
ALT increased	49 (13.2)	13 (13.3)	41 (9.6)	77 (14.5)	36 (13.1)	21 (10.9)
AST increased	41 (11.0)	15 (15.3)	59 (13.8)	70 (13.1)	26 (9.5)	16 (8.3)
SAEs overall incidence	0	0	2 (0.5)	2 (0.4)	0	0
% discontinuation	5 (1.3)	0	4 (0.9)	8 (1.5)	5 (1.8)	5 (2.6)
% dose change/interruption	31 (8.3)	8 (8.2)	13 (3.0)	50 (9.4)	23 (8.4)	15 (7.8)
% additional therapy	6 (1.6)	1 (1.0)	4 (0.9)	7 (1.3)	5 (1.8)	4 (2.1)
EAIR (PT) [2]	2.05	1.58	4.74	2.42	2.21	2.03

Source: ISS Table 2.1.27.1, Table 2.1.27.2 and Table 2.1.27.3
Sources: W00090_NSCLC - Version date: 25JUL2023 12:22 - File Name: Sub5_3_6_c1_RMPLiverEnBi_saf_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADADR:24JUL2023 ADSP1.ADSL:27JUN2023 - PGM Sub5_3_6_c1_RMPLiverEnBi_saf_t.sas 30JUN2023 12:29
[1] PT with incidence ⩾5% in any population
[2] EAIR (Exposure adjusted incidence rate per 100 patient-months) = (n*100)/(total exposure time in months).
A patient with multiple adverse events within a preferred term is counted only once in that preferred term.
MedDRA Version 25.1 has been used for the reporting of adverse events
* Note: In Pharos study (ARRAY-818-202), GGT values were not monitored except if clinically indicated, whereas in Melanoma studies GGT values were monitored at each cycle up to the Safety Follow-up visit.

In the post-marketing experience, cumulatively up to 26 June 2023 (DLP of the most recent PSUR), 349 cases were identified in the global safety database (representing 6.8% of all post-marketing cases) reporting 451 events indicative for hepatotoxicity. Of them, 188 were serious. The PTs most frequently reported included alanine aminotransferase increased (57 events), aspartate aminotransferase increased (52 events), hepatic function abnormal, liver disorder (46 events each), hepatic enzyme increased (39 events), Gamma-glutamyltransferase increased (36 events), liver function test increased (24 events), hepatic cytolysis (21 events), hepatitis (15 events), transaminases increased (14 events), drug-induced liver injury, liver function test abnormal (13

events each), hepatotoxicity (12 events), and hepatic failure (7 events). These cases concerned 169 female patients and 154 male patients while the gender was not reported in 26 cases, the reported mean age was 61.6 years.

Absolute risks

The absolute risk of liver function test abnormalities in the Bini 45 P population was 0.173 and 0.042 for Grade 3 to 4.

With regard to the most relevant liver laboratory parameter (ALT), the absolute risk of ALT elevation in the Bini 45 P was 0.096 and 0.023 for Grade 3 to 4 events.

The absolute risk of overall liver laboratory test abnormalities in the Combo 450 RP (Melanoma population) was 0.263 and 0.124 for Grade 3 to 4 events.

The absolute risk of ALT increased in the Combo 450 RP (Melanoma population) was 0.131 and 0.033 for Grade 3 to 4 events.

Relative risks as compared with "unexposed" patient populations

In order to perform the RR calculations, a literature search was undertaken to identify European studies reporting the risk of hepatotoxicity in real-world, BRAF-mutated metastatic melanoma patients who were unexposed to binimetinib single agent or to any interventions in the same therapeutic class (i.e. any MEK inhibitor for binimetinib single agent).

The identified studies and the results of the RR calculations are presented in the table below. No studies with a relevant "unexposed" patient population were identified for the purposes of the encorafenib and binimetinib RR calculation; therefore, no RR calculations could be performed for this regimen.

In order to perform the RR calculations, a literature search was undertaken to identify European studies reporting the risk of hepatotoxicity in real-world, BRAF-mutated metastatic NSCLC patients who were unexposed to binimetinib single agent or to any interventions in the same therapeutic class (i.e. any MEK inhibitor for binimetinib single agent).

No studies reporting the risk of hepatotoxicity in a relevant "unexposed" patient population were identified for the purposes of the binimetinib single agent RR calculations; No RR calculations could be performed for this regimen.

Table SVII.9: Relative risks of liver enzymes increased as compared with "unexposed" patient populations

Relative risk									
Adverse event as described in data source	**Source of "unexposed" population incidence**	**Population description**	**Risk reported**	**Study location**	**Treatment(s)**	**N population**	**Number of patients experiencing event**	**Absolute risk in "unexposed" population**	**Relative risk for Bini vs unexposed**
Liver enzyme AEs (ALT increased), all grades	Ocvirk *et al*. 2015 [CMC ID 964]	Metastatic melanoma, BRAF V600E or V600K	Grade 1-4 elevated liver enzymes	Slovenia	Vemurafenib	39	6	0.154	0.624
	Sponghini *et al*. 2014	BRAF V600E+ metastatic melanoma (stage IV)	Elevated liver enzymes (no more detail provided)	Italy	Vemurafenib	16	1	0.063	1.536
Liver enzyme AEs (ALT increased), grade 3/4	Kramkimel *et al*. 2016	Advanced metastatic melanoma with BRAF V600E and other V600E mutations	≥ grade 3 liver function abnormalities	France	Vemurafenib	59	2	0.034	0.679
	Ocvirk *et al*. 2016	Metastatic melanoma, BRAF V600E or V600K	Grade 3-4 liver injury	Slovenia	Vemurafenib	65	2	0.031	0.748
	Ocvirk *et al*. 2015 [CMC ID 964]	Metastatic melanoma, BRAF V600E or V600K	Grade 3-4 elevated liver enzymes	Slovenia	Vemurafenib	39	2	0.051	0.449

Seriousness:

In melanoma patients in the Bini 45 P population (N=427), SAEs of liver events were reported in 6 (1.4%) patients (PTs of ascites [2 (0.5%) patients]; AST increased [2 (0.5%) patients]; and ALT increased, GGT increased, hepatic failure, and hepatic pain [1 (0.2%) patient each] (Table RMP2.1-14 and Table RMP2.2-14).

In Study CMEK162A2301, liver events were reported as SAEs for 3 (1.1%) patients in the binimetinib arm, including events by PT of ALT increased, AST increased, ascites and hepatic failure (1 (0.4%) patients each) (Table RMP2.214).

In the Combo 450 ISP, SAE of liver events were reported in 1 patient (PT: Hepatic failure). This event was reported in the Combo 450 RP (Melanoma population). No SAE of liver events was reported in the NSCLC population.

Severity:

Grade 3/4 liver events were reported in 23 (5.4%) and 14 (5.2%) patients in the all melanoma Bini 45 P population and in the binimetinib arm of Study CME Work in progress K162A2301, respectively (Table RMP2.1-14).

There have been no identified cases of Hy's law due to binimetinib. Based on abnormal liver function tests, 3 patients potentially fulfilled the criteria for Hy's law and required further analysis; it was determined after this analysis that these patients did not meet the criteria for Hy's Law.

Grade ≥ 3 cases of liver laboratory test abnormalities occurred at a frequency of 11.4% and 11.8% respectively in the Combo broad ISP population and the Combo 450 ISP (12.4% in the Combo 450 RP; 14.1% in Combo 450 arm of study CMEK162B2301, and 10.2% in the NSCLC population).

Liver laboratory test abnormalities led to discontinuation of the combination at a frequency of 1.5%, 1.3% and 2.6% respectively in the Combo 450 broad ISP population, Combo 450 ISP and Combo 450 arm of study CMEK162B230.

Dose adjustment occurred at a frequency of 9.4%, 8.3% and 7.8% respectively in the Combo broad ISP population, Combo 450 ISP and Combo 450 arm of study CMEK162B230 while additional treatment was needed in 1.3%, 1.6% and 2.1% of the cases respectively.

There were no cases meeting the case finding criteria of Hy's law in the Combo 450 populations.

Outcome:

Summary of event outcome for transaminases increased is provided below:

Table SVII.10: Encorafenib and binimetinib combination: Adverse event outcome for ALT and AST increased events

Preferred Term	**Outcome Status [1]**	**Combo 450 ISP N=372 n (%)**	**Study CMEK162B2301 Combo 450mg QD N=192 n (%)**
ALT increased overall	Recovered/Resolved	37/49 (75.5)	20/21 (95.2)
	Recovering/Resolving	1/49 (2.0)	0
	Not Recovered/Not resolved	5/49 (10.2)	1/21 (4.8)
	Unknown	6/49 (12.2)	0
ALT increased Grade≥3	Recovered/Resolved	14/18 (77.8)	5/5 (100)
	Recovering/Resolving	1/18 (5.6)	0
	Not Recovered/Not Resolved	2/18 (11.1)	0
	Unknown	1/18 (5.6)	0
AST increased overall	Recovered/Resolved	34/41 (82.9)	15/16 (93.8)
	Not Recovered/Not resolved	5/41 (12.2)	1/16 (6.3)
	Unknown	2/41 (4.9)	0
AST increased Grade≥3	Recovered/Resolved	11/13 (84.6)	2/2 (100)
	Recovering/Resolving	1/13 (7.7)	0
	Not Recovered/Not Resolved	1/13 (7.7)	0

Sources: ISS Part1_u. Table 2.6.81b
Sources: W00090_NSCLC - Version date: 25JUL2023 12:15 - File Name: Sub5_1_6_c1_RMPAdrOutSum_treat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADADR:24JUL2023 ADSP1.ADSL:27JUN2023 - PGM Sub5_1_6_c1_RMPAdrOutSum_treat_t.sas 04MAY2023 11:16
N represents the number of patients in the considered PT, a patient is counted once by PT.
[1] For each patient, the last collected status of the outcome by PT is considered.
The worst case scenario was taken when there were 2 outcomes at the same date for the same PT
MedDRA Version 25.1 was used for the reporting of adverse events.

Reversibility

During clinical trials in oncology, hepatotoxicity was managed based on clear dose modification/discontinuation instructions based on laboratory and clinical monitoring. Detailed recommendations have been published (Welsh 2015). This includes that liver blood tests (transaminases, ALP, and bilirubin) should be monitored before the initiation of BRAF and/or MEK inhibitor therapy, and monthly throughout the duration of treatment, or as clinically indicated (Welsh 2015). In addition, dose reduction, medication switch, temporary therapy suspension or permanent discontinuation may be recommended based on the severity of observed liver abnormalities, as well as referral or review by a hepatology specialist. In most cases, drug dose modification or discontinuation leads to an improvement in liver biochemistries and reversal of the hepatoxicity.

Long-term outcomes

While long-term results are not available at this time, the impact of the risk of hepatotoxicity on the individual patient is thought to be low with regular monitoring, and because drug modification or discontinuation can reverse hepatotoxicity (Leise 2014; Shah 2013). More serious liver abnormalities, however, such as bilirubin levels of more than 3 g/dL, have been shown to be associated with mortality rates of at least 10% (Leise 2014), suggesting a wide range of potential long-term outcomes with MEK inhibitor therapy. However, due to the life-expectancy in the metastatic treated diseases, the potential for a liver injury to develop into a chronic form of liver disease such as cirrhosis is unlikely.

Impact on quality of life

Hepatotoxicity may have a serious impact on the quality of life of the individual patient, including death, though this may be mitigated by early identification and management of the symptoms. If managed according to local standards of care with proper monitoring and investigations, it can be expected that liver biochemical parameters return to normal following drug modification or discontinuation, hence a long-term impact on patient quality of life is not anticipated in most cases (Leise 2014).

Risk factors and risk groups:

In the binimetinib clinical studies (binimetinib single agent), hepatic toxicities were reported more frequently in patients with liver metastasis when compared to the overall patient population. In the Bini 45 P population, an increase of ALT >3 × ULN (a measure of hepatic toxicity) was reported more frequently in patients with liver metastasis when compared to the overall patient population and to patients with no liver metastasis (12/131 (9.2%), 28/414 (6.8%), and 16/283 (5.7%) patients, respectively) (ISS Table 3.2-2). There were no other remarkable differences in liver parameters according to the presence of baseline metastases.

Preventability:

This risk may be prevented through physician awareness: Monitoring of liver enzyme tests will be performed as part of routine care of unresectable and metastatic melanoma patients and advanced NSCLC patients as the liver is one of the most frequent locations of cancer metastases. Therefore, liver function testing would likely be performed routinely, irrespective of the suspected hepatotoxicity. Please see PART V for further details.

Impact on the benefit-risk balance of the product:

The risk of hepatotoxicity should be satisfactorily minimised through the routine risk minimisation measures described in PART V.

Public health impact (Expected population outcome):

EUCAN data from 2012 indicate an age standardised incidence rate of malignant melanoma of the skin in the EU of 13.0 per 100,000 of population per year (European Cancer Information System*).* There are currently 508 million individuals living in the EU (European Commission). Assuming that 20% of diagnosed melanomas progress to a metastatic stage, and that approximately 50% of these cases are positive for BRAF V600E mutation (Ascierto 2012), the target population is estimated to be approximately 6,552 individuals per year.

Given the absolute risk in the Bini 45 P population of:

- Liver function abnormalities described above for patients treated with binimetinib alone (0.194) in the Bini 45 P population, an estimated 1,271 patients receiving this therapeutic regimen may be expected to develop liver function abnormalities in a population of 6,552 eligible patients each year.
- Severe (Grade 3/4) liver function abnormalities described above for patients treated with binimetinib alone (0.054), an estimated 354 patients receiving this therapeutic regimen may be expected to develop severe liver function abnormalities in a population of 6,552 eligible patients each year.
- ALT elevation (considered more specific than AST which can be influenced by muscular changes) all grades described above for patients treated with binimetinib alone (0.096), an estimated 629 patients receiving this therapeutic regimen may be expected to develop severe liver function abnormalities in a population of 6,552 eligible patients each year if all are treated.
- Severe ALT elevation (Grade 3/4) described above for patients treated with binimetinib alone (0.023), an estimated 151 patients receiving this therapeutic regimen may be expected to develop severe liver function abnormalities in a population of 6,552 eligible patients each year if all are treated.

In Europe, using the estimated value of 477,500 new cases of lung cancer diagnosed in 2020 (Dyba, 2021), and assuming that about 80% of newly diagnosed lung cancers are NSCLC (American Cancer Society, 2021), with 60% of NSCLC patients are diagnosed at advanced stage (stages IIIB/C and IV), and approximately 3% of them are positive for BRAF mutations with 50% of them driven by the BRAF V600E mutation (Class 1), it can be estimated that approximately 3,438 individuals presented with BRAF V600E-mutated advanced lung cancer in 2020 across EU countries.

Given the absolute risk in the Bini 45 P population of:

- Liver function abnormalities described above for patients treated with binimetinib alone (0.194) in the Bini 45 P population, an estimated 667 patients receiving this therapeutic regimen may be expected to develop liver function abnormalities in a population of 3,438 eligible patients each year.
- Severe (Grade 3/4) liver function abnormalities described above for patients treated with binimetinib alone (0.054), an estimated 186 patients receiving this therapeutic regimen may be expected to develop severe liver function abnormalities in a population of 3,438 eligible patients each year.
- ALT elevation (considered more specific than AST which can be influenced by muscular changes) all grades described above for patients treated with binimetinib alone (0.096), an estimated 330 patients receiving this therapeutic regimen may be expected to develop severe liver function abnormalities in a population of 3,438 eligible patients each year if all are treated.
- Severe ALT elevation (Grade 3/4) described above for patients treated with binimetinib alone (0.023), an estimated 79 patients receiving this therapeutic regimen may be expected to develop severe liver function abnormalities in a population of 3,438 eligible patients each year if all are treated.

It is to be noted however, that safety data from clinical trials may not be necessarily extrapolated to the real-world target population, as patients enrolled in clinical trials from a specific, controlled subset of patients fulfilling strict inclusion criteria, without severe comorbidities and certain concomitant medications.

(iv) Important potential risk: Pneumonitis/Interstitial lung disease (ILD)

Potential mechanisms:

The underlying mechanism for these events, considered to be a MEK inhibitor class effect is not yet known. It has been hypothesised that the blockage of EGFR-dependent epithelial proliferation by EGFR-TKIs augments pulmonary fibrosis (Min 2011; Suzuki 2003). Interstitial lung disease including pneumonitis has occurred with treatment with MEK inhibitors, as trametinib; the pathophysiology of these disorders is currently unclear, but involvement of the MAPK/ERK pathway itself is one hypothesis (Giraud 2015).

Evidence source and strength of evidence:

The ADR of pneumonitis/ILD is a known class effect of MEK inhibitors. There may be a causal association of binimetinib for this potential risk.

Characterisation of the risk:

Frequency with 95% CI:

In melanoma patients in the Bini 45 P population (N=427), pneumonitis events were reported in 1.4% of patients. The most frequently reported PTs were pneumonitis (4 (0.9%) patients) and interstitial lung disease (2 (0.5%) patients).

In the binimetinib arm in Study CMEK162A2301, the most frequently reported PT was pneumonitis (3 (1.1%) patients) (Table RMP2.1-16, Table RMP2.2-16).

Table SVII.11: Summary of pneumonitis/ILD Events (Bini 45 P)

	All Melanoma
Pneumonitis Events	**Bini 45 P N=427 n (%)**
Overall incidence	6 (1.4)
Grade 3 to 4	3 (0.5)
PT with incidence >10%	None
SAEs overall incidence	4 (0.9)
AEs leading to discontinuation	2 (0.5)
AEs leading to dose change/reduction/interruption	1 (0.2)

Sources: ISS-PART 1_U Table 2.1.20.1-u, ISS-PART 1_U Table 2.1.20.2-u
A patient with multiple occurrences is counted only once with the maximum reported severity.
MedDRA Version 19.0 was used for the reporting of adverse events.
Events included (PTs): Acute respiratory distress syndrome, interstitial lung disease, pneumonitis.

In the initial MAA, pneumonitis events were reported at a very low overall incidence in the Bini P and Combo 450 RP (Melanoma) populations (1.4%-0.32 case per 100 patient-months vs 0.4%-0.03 case per 100 patient-months). Few events were Grade 3/4 (0.5% vs none) or serious (0.7% vs none), led to study drug discontinuation (0.5% vs none), required dose adjustment/study drug interruption (0.2% vs 0.4%) or additional therapy (1.2% vs 0.4%). 1 patient in the Combo 450 arm of Study CMEK162B2301 experienced a non serious event of Grade 2 pneumonitis, which required dose adjustment/study drug interruption and additional therapy.

In the NSCLC population, pneumonitis events were reported in 2 patients (2.0%), both events were Grade 1 and non-serious. None required study drug discontinuation, additional therapy or dose adjustment/study drug interruption.

Pneumonitis/ILD was not determined as an ADR in the Combo 450 ISP, based on the available data. However, it is considered as a potential safety concern in this setting.

In the post-marketing experience, cumulatively up to 26 June 2023 (DLP of the most recent PSUR), 29 cases were identified in the global safety database (representing 0.6 % of all post-marketing cases) reporting 33 events indicative for pneumonitis/ILD. Of them, 29 were serious. The relevant reported PTs included interstitial lung disease (14 events), pneumonitis (12 events), lung opacity, pulmonary toxicity (2 events each), eosinophilic granulomatosis with polyangiitis, lung infiltration, and pulmonary fibrosis (1 event each). These cases reported in 9 female patient and 17 male patients, while the geneder was not reported in 3 cases. reported mean age was 64.2 years. No new safety information was identified for binimetinib and pneumonitis/ILD based on the cumulative post-marketing data.

Absolute risks

The absolute risk of pneumonitis events in the Bini 45 P was 0.014.

Relative risks as compared with "unexposed" patient populations

In order to perform the RR calculations, a literature search was undertaken to identify European studies reporting the risk of pneumonitis in real-world, BRAF-mutated metastatic melanoma patients who were unexposed to binimetinib single agent, or to any interventions in the same therapeutic class (i.e. any MEK inhibitor for binimetinib single agent).

No studies reporting the risk of pneumonitis in a relevant "unexposed" patient population were identified for the purposes of the binimetinib single agent RR calculations; therefore, no RR calculations could be performed.

In order to perform the RR calculations, a literature search was undertaken to identify European studies reporting the risk of pneumonitis in real-world, BRAF-mutated metastatic NSCLC patients who were unexposed to binimetinib single agent, or to any interventions in the same therapeutic class (i.e. any MEK inhibitor for binimetinib single agent).

Patients with lung cancer may be predisposed to the development of drug-induced pulmonary toxicity as they have higher rates of pre-existing lung pathology, such as emphysema or ILD, and higher rates of smoking history. In a meta-analysis of patients treated with docetaxel and gemcitabine for multiple types of cancer, Binder et al. found that patients with lung cancer were significantly more likely to develop pulmonary toxicity than patients with breast cancer; however, the risk did not remain significant when compared with all other types of cancers studied (Binder et al, 2011).

No studies reporting the risk of pneumonitis in a relevant "unexposed" patient population were identified for the purposes of the binimetinib single agent RR calculations; therefore, no RR calculations could be performed.

Seriousness:

In melanoma patients in the Bini 45 P population (N=427), SAEs in the pneumonitis events grouping were reported for 4 (0.9%) patients (PTs of pneumonitis [2 (0.5%) patients], and acute respiratory distress syndrome and interstitial lung disease [1 (0.2%) patient each]) (Table RMP2.1-16 and Table RMP2.2-16). Since the search strategy also identified AEs which describe symptoms but not pneumonitis, the focus is on AEs described by PT Pneumonitis or interstitial lung disease. Three (3) of those SAEs describe pneumonitis. A review of other events confirmed that they do not describe the clinical concept of pneumonitis.

In the binimetinib arm of Study CMEK162A2301, SAEs in the pneumonitis events grouping were reported for 2 (0.7%) patients (both PTs of pneumonitis) (Table RMP2.1-16 and Table RMP2.2-16).

One (0.2%) patient from Study CMEK162X2201 reported an SAE coded with the individual PT of ILD.

No SAE of pneumonitis occurred in the Combo 450 ISP.

Severity:

Grade 3/4 AEs in the pneumonitis events grouping were reported for 3 (0.7%) and one (0.4%) patient in the all melanoma Bini 45 P population and in the binimetinib arm of Study CMEK162A2301, respectively (Table RMP2.1-16).

Kaplan-Meier plots of time to first Grade ≥2 pneumonitis event showed a median time to onset of 2.5 months each for binimetinib-treated patients in Study CMEK162A2301 and the all melanoma [binimetinib 45 mg] population (ISS Figure 2.1-11A).

No Grade ≥ 3 event of pneumonitis occurred in the Combo 450 populations.

One non serious event of Grade 2 pneumonitis, which required study drug interruption and additional therapy, occurred in the Combo 450 arm of Study CMEK162B2301.

Outcome:

Table SVII.12: Pneumonitis adverse event outcome status (CMEK162A2301)

		Melanoma
PT	**Outcome Status**	**Binimetinib 45 mg BID N=269* n (%)**
Pneumonitis overall	Recovered/Resolved	2/3 (66.7)
	Recovered/Resolved with sequelae	0
	Recovering/Resolving	0
	Unknown/Missing	0
	Not Recovered/Not resolved	1/3 (33.3)
	Ongoing	0
	Fatal	0

Sources: ISS Supp: Table 2.6.8.2a.
Melanoma: Naive to BRAF inhibitors and MEK inhibitors. A patient is counted once within each PT and ADR grouping.

For each patient, the last collected status of the outcome by PT is considered. The worst-case scenario was taken when there were 2 outcomes at the same date for the same PT, ranging: 'Fatal', 'Ongoing', 'Not Recovered/Not Resolved', 'Unknown/Missing', 'Recovering/Resolving', 'Recovered/Resolved with Sequelae', 'Resolved'.
Ongoing outcomes represent the 'Not Recovered/Not Resolved' outcomes at the study cut-off date.
*The study CMEK162X2201 was excluded because the outcome status was not collected.

Of note, pneumonitis/ILD was not determined as an ADR in combination use of binimetinib including in the Combo 450 ISP, based on the available data.

Reversibility

In the absence of specific consensus guidelines on the management of pneumonitis rising from MEK inhibitor treatment in metastatic melanoma patients, pneumonitis should be managed per local guidelines. Patients experiencing cough, shortness of breath, or abnormal chest signs should be investigated with a plain chest X-ray or chest computed tomography scan (Welsh 2015). Pneumonitis developing from treatment can be managed by dose reduction or discontinuation of MEK inhibitor treatment and, dependent on the severity of the pneumonitis, commencing high-dose corticosteroids (Welsh 2015). In severe cases, oxygen can be provided. If there is life-threatening respiratory compromise, further interventions such as tracheotomy or intubation may be necessary (Welsh 2015).

Long-term outcomes

While long-term results are not available at this time, the impact of the risk of pneumonitis on the individual patient can be serious dependent on the severity and progression of the pulmonary symptoms. For patients developing pneumonitis on a MEK inhibitor, recovery is possible following treatment modification or discontinuation, and correct management (Welsh 2015). However, outcomes can be dependent on the severity and progression of symptoms, resulting in the potential for a long-term effect.

Impact on quality of life

Pneumonitis is likely to have a range of impacts on the quality of life of the individual patient depending on symptom severity and progression. If mild, pneumonitis can be asymptomatic and reversible if correct monitoring and management is undertaken, therefore only impacting quality of life temporarily. More severe and progressive pneumonitis and pulmonary symptoms can result in hospitalisation and possibly even death, therefore having a substantial impact on a patient's quality of life.

Risk factors and risk groups:

Among the 3 patients reporting events with PT Pneumonitis in Study CMEK162A2301, 2 had lung metastasis and the third had history of pneumonitis.

Drug-induced interstitial lung disease is reported to occur with higher frequency in the Asian population (Peerzada 2011).

Preventability:

This risk may be prevented through physician awareness, patient information and early identification of signs and symptoms. Early reporting of respiratory symptoms should lead to evaluation of cause and consideration of discontinuation or withholding of dosing if no alternative cause is found. Please see PART V for further details.

Impact on the benefit-risk balance of the product:

The risk of pneumonitis potentially should be satisfactorily minimised through the routine risk minimisation measures described in PART V.

Public health impact (Expected population outcome):

EUCAN data from 2012 indicate an age standardised incidence rate of malignant melanoma of the skin in the EU of 13.0 per 100,000 of population per year (European Cancer Information System*).* There are currently 508 million individuals living in the EU (European Commission). Assuming that 20% of diagnosed melanomas progress to a metastatic stage, and that approximately 50% of these cases are positive for BRAF V600E mutations (Ascierto 2012), the target population is estimated to be approximately 6,552 individuals per year.

Given the absolute risk of pneumonitis events described above for patients treated with binimetinib alone (0.014), an estimated 92 patients receiving this therapeutic regimen may be expected to develop pneumonitis in a population of 6,552 eligible patients each year if all are treated.

In Europe, using the estimated value of 477,500 new cases of lung cancer diagnosed in 2020 (Dyba, 2021), and assuming that about 80% of newly diagnosed lung cancers are NSCLC (American Cancer Society, 2021), with 60% of NSCLC patients are diagnosed at advanced stage (stages IIIB/C and IV), and approximately 3% of them are positive for BRAF mutations with 50% of them driven by the BRAF V600E mutation (Class 1), it can be estimated that approximately 3,438 individuals presented with BRAF V600E-mutated advanced lung cancer in 2020 across EU countries.

Given the absolute risk of pneumonitis events described above for patients treated with binimetinib alone (0.014), an estimated 48 patients receiving this therapeutic regimen may be expected to develop pneumonitis in a population of 3,438 eligible patients each year if all are treated.

It is to be noted however, that safety data from clinical trials may not be necessarily extrapolated to the real-world target population, as patients enrolled in clinical trials from a specific, controlled subset of patients fulfilling strict inclusion criteria, without severe comorbidities and certain concomitant medications.

SVII.3.2 Presentation of missing information

(i) Missing information for binimetinib

None.

Part II: Module SVIII - Summary of the safety concerns of binimetinib

The following table summarises safety concerns for binimetinib in combination use.

No safety concerns have been identified for binimetinib when combined with encorafenib, in addition to the safety concerns of binimetinib single agent.

Table SVIII.1: Summary of safety concerns for binimetinib in combination with encorafenib

Important identified risks	- Left ventricular dysfunction - Haemorrhage - Hepatotoxicity
Important potential risks	- Pneumonitis/Interstitial lung disease
Missing information	- None

PART III : PHARMACOVIGILANCE PLAN

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond ADR reporting and signal detection:

Specific adverse reaction 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 adverse reactions follow up forms for binimetinib are provided in Annex 4:

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

III.2 Additional pharmacovigilance activities

No non-clinical, clinical, epidemiological or post-authorisation safety studies (PASS) are planned at the time of this RMP.

III.3 Summary table of additional pharmacovigilance activities

None

PART IV: Plans for post-authorisation efficacy studies

There are no planned or ongoing imposed post-authorisation efficacy studies.

PART V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine risk minimisation measures

The table presented below includes the description of routine risk minimisation measures by safety concern for binimetinib in combination use.

Table Part V.1: Description of routine risk minimisation measures by safety concern for binimetinib in combination with encorafenib

Safety concern	Routine risk minimisation activities
Important identified risks for binimetinib in combination with encorafenib	
Left ventricular dysfunction	**Routine risk communication:** Proposed text in the SmPC. • Dose modification recommendations are provided in Section 4.2 of the SmPC. • Warning is provided in Section 4.4 of the SmPC and relevant Package Leaflet (PIL) section. • Listed in Section 4.8 of the SmPC and relevant PIL section. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Section 4.4 of the SmPC: It is recommended that LVEF is assessed by echocardiogram or MUGA scan before initiation of binimetinib, 1 month after initiation, and then at ~3-month intervals or less while on treatment. The occurrence of LVEF can be managed with treatment interruption, dose reduction or with treatment discontinuation. In patients with a baseline LVEF that is either below 50 % or below the institutional LLN, binimetinib should be discontinued for any symptomatic left ventricular dysfunction, Grade 3-4 LVEF, or absolute decrease of LVEF from baseline of ≥ 10 %, and LVEF evaluated every 2 weeks until recovery. **Other risk minimisation measures beyond the Product Information:** Pack size: NA Medicine's legal status: 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.
Haemorrhage	**Routine risk communication:** Proposed text in the SmPC. • Dose modification recommendations are provided in Section 4.2 of the SmPC. • Warning is provided in Section 4.4 of the SmPC and relevant PIL section. • Listed in Section 4.8 of the SmPC and relevant PIL section.

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.4 of the SmPC: Potential for increased risk of haemorrhage with concomitant use of antiplatelet or anticoagulant therapy. **Other risk minimisation measures beyond the Product Information:** Pack size: NA Medicine's legal status 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.
Hepatotoxicity	**Routine risk communication:** Proposed text in the SmPC. • Dose modification recommendations are provided in Section 4.2 of the SmPC. • Warning is provided in Section 4.4 of the SmPC and relevant PIL section. • Listed in Section 4.8 of the SmPC and relevant PIL section. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Section 4.4 of the SmPC: Liver laboratory tests should be monitored before initiation of binimetinib and at least monthly during the first 6 months of treatment, and as clinically indicated. Liver laboratory abnormalities should be managed with dose interruption, reduction, or discontinuation of binimetinib. **Other risk minimisation measures beyond the Product Information:** Pack size: NA Medicine's legal status: 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.
Important potential risks for binimetinib in combination with encorafenib	
Pneumonitis/Interstitial lung disease	**Routine risk communication:** Proposed text in the SmPC. • Dose modification recommendations are provided in Section 4.2 of the SmPC. • Warning is provided in Section 4.4 of the SmPC and relevant PIL section. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Section 4.4 of the SmPC: Treatment with binimetinib should be withheld in patients with suspected pneumonitis/ILD diagnosis including new or progressive

Safety concern	Routine risk minimisation activities
	pulmonary symptoms or findings, such as cough, dyspnoea, hypoxia, reticular opacities, or pulmonary infiltrates, and permanently discontinued in patients diagnosed with treatment-related pneumonitis or ILD. **Other risk minimisation measures beyond the Product Information:** Pack size: NA Medicine's legal status 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.
Missing information for binimetinib in combination with encorafenib	
None	

V.2. Additional Risk Minimisation Measures

No additional risk minimisation measures have been identified.

V.3 Summary of Risk Minimisation Measures

The table presented below includes the summary of pharmacovigilance activities and risk minimisation activities for safety concerns of binimetinib in combination with encorafenib.

Table Part V.3: 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.	Routine: specific Haemorrhage ADR follow-up form. Additional: none.

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
	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.	
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
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		

PART VI: Summary of the risk management plan

Summary of the risk management plan for MEKTOVI

This is a summary of the risk management plan (RMP) for MEKTOVI in combination with BRAFTOVI. The RMP details important risks of MEKTOVI in combination with BRAFTOVI, how these risks can be minimised, and how more information will be obtained about MEKTOVI in combination with BRAFTOVI risks and uncertainties (missing information).

The summary of product characteristics (SmPC) for MEKTOVI and its package leaflet give essential information to healthcare professionals and patients on how MEKTOVI should be used.

This summary of the RMP for MEKTOVI in combination with BRAFTOVI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to current concerns will be included in updates of the RMP for MEKTOVI.

I. The Medicine and what it is used for

MEKTOVI in combination with BRAFTOVI is authorised for the treatment of adult patients with unresectable or metastatic melanoma, with BRAF V600 mutation (see SmPC for the full indication). The active substance of MEKTOVI is binimetinib and of BRAFTOVI is encorafenib, and both are given by the oral route of administration.

MEKTOVI in combination with BRAFTOVI is proposed for the treatment of adult patients with BRAF V600E mutant advanced non-small cell lung cancer (NSCLC). Both drugs are given by the oral route.

MEKTOVI is not authorised for use as a single agent.

Further information about the evaluation of MEKTOVI in combination with BRAFTOVI can be found in the MEKTOVI and BRAFTOVI EPARs, including a plain-language summary, available on the EMA website, under the medicine's webpage <*link to the EPAR summary landing page*>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of MEKTOVI in combination with BRAFTOVI, together with measures to minimise such risks and the proposed studies for learning more about MEKTOVI in combination with BRAFTOVI, are outlined below.

Measures to minimise the risks identified for medicinal products include:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the packaging of the medicine;
- The authorised pack size - the amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly;
- The legal status of the medicine- the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimises its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessments, so that immediate action can be taken and updates made as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of MEKTOVI in combination with BRAFTOVI are risks that need risk management activities to further investigate or minimise the risk, so that the medicinal product can be taken safely. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of MEKTOVI in combination with BRAFTOVI. Potential risks are concerns for which an association with the use of these medicines is possible based on available data, but this association has not yet been established and needs further evaluation.

Missing information refers to information on the safety of MEKTOVI as a single agent or in combination with BRAFTOVI that is currently missing and needs to be collected.

Table Part VI.1: Safety concerns for binimetinib in combination with encorafenib

Important identified risks	- Left ventricular dysfunction - Haemorrhage - Hepatotoxicity
Important potential risks	- Pneumonitis/Interstitial lung disease
Missing information	- None

II.B Summary of important risks and missing information

Important identified risk: Left ventricular dysfunction	
Description of the risk title	Heart problems, e.g. a drop in the amount of blood pumped by the heart.
Evidence for linking the risk to the medicine	Left ventricular dysfunction is an identified ADR for binimetinib. Left ventricular dysfunction is a known effect of MEK inhibitors, a class of drugs to which binimetinib belongs. There is sufficient scientific evidence to suspect a causal association between binimetinib and this risk.
Risk factors and risk groups	Patients with significant heart problems were excluded from the binimetinib clinical trials. Among the patients who were included in the binimetinib clinical studies, no risk groups or factors have been identified. LVEF shift data were assessed in patients with or without baseline cardiovascular risk factors (defined as current/ex-smoker and/or history of hypertension, diabetes, hyperlipidaemia [raised cholesterol], cardiac disorders, arteriosclerosis [thickening of the walls of arteries] and ischemic heart disease [coronary heart disease]) with most patients having baseline risk factors. These data showed no difference in the percent of patients LVEF shifts for patients with worst postbaseline LVEF by baseline cardiac risk factor category 'yes' or 'no'.
Risk minimisation measures	Routine risk minimisation measures: 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 risk minimisation measures: None
Important identified risk: Haemorrhage	
Description of the risk title	A large flow of blood from a damaged blood vessel
Evidence for linking the risk to the medicine	Haemorrhage is a known class effect of MEK inhibitors. ADRs in the grouped term of haemorrhage were reported as common for binimetinib. There is sufficient scientific evidence to suspect a causal association between binimetinib and this risk.
Risk factors and risk groups	Specific risk groups have not been identified based on binimetinib trials. Patients receiving antiplatelet and anticoagulant medications in combination with any other treatment which may cause bleeding are at greater risk of haemorrhage.
Risk minimisation measures	Routine risk minimisation measures: 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 risk minimisation measures: None.
Important identified risk: Hepatotoxicity	
Description of the risk title	Liver problems
Evidence for linking the risk to the medicine	There is sufficient scientific evidence to suspect a causal association between binimetinib and this risk and abnormal liver enzymes and hepatotoxicity. ALT and AST increased are class effects related to MEK inhibitors and elevation of liver enzymes is an identified ADR for binimetinib.
Risk factors and risk groups	In the binimetinib clinical studies, hepatic events were reported more frequently in patients with liver metastasis when compared to the overall patient population. In the Bini 45 P, an increase of ALT >3 × ULN (a measure of hepatic toxicity) was reported more frequently in patients with liver metastasis when compared to the overall patient population and to patients with no liver metastasis (12/131 [9.2%], 28/414 [6.8%], and 16/283 [5.7%] patients, respectively). There were no other remarkable differences in liver parameters according to the presence of baseline metastases.
Risk minimisation measures	Routine risk minimisation measures: 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 risk minimisation measures: None
Important potential risk: Pneumonitis/Interstitial Lung Disease (ILD)	
Description of the risk title	Inflammation inside the lungs
Evidence for linking the risk to the medicine	Pneumonitis/ILD is a known class effect of MEK inhibitors. There may be a causal association of binimetinib for this potential risk.
Risk factors and risk groups	Specific risk groups have not been identified based on binimetinib trials. Pneumonitis was reported in 3 patients in Study CMEK162A2301 and was associated with lung metastases in 2 patients, and history of pneumonitis was reported in the third patient. Drug-induced interstitial lung disease is reported to occur with higher frequency in the Asian population (Peerzada 2011).
Risk minimisation measures	Routine risk minimisation measures: 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 risk minimisation measures: None.
Missing Information	None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

None.

II.C.2 Other studies in post-authorisation development plan

None.

PART VII: ANNEXES

Annex 4 - Specific adverse drug reaction follow-up forms

Specific adverse reaction 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 encorafenib

The following specific adverse reactions follow up forms for binimetinib are provided in this annex:

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

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ADVERSE DRUG REACTION COLLECTION FORM - BRAFTOVI AND MEKTOVI COMBINATION - CARDIAC DYSFUNCTION

File n°: |__|__|__|__| - |__|__|__|__|__| *(For department use only - Make no entry in this space)*

Reporter's information[III]:

Name:	❑ Healthcare Professional: ❑ Physician ❑ Pharmacist ❑ Other: _____
Address:	
Tel:	❑ Patient ❑ Other: .....

Patient identification

First Name (first 3 letters): |__|__|__| Last Name (first 2 letters): |__|__|

Date of birth: _____ or Age: _____ Gender: _____ Weight: _____ Height: _____

Medical cardiovascular history:

Baseline LVEF: _____% (Lower Limit Normal = _____)

Heart failure, NYHA: _____ ☐ Onset date ___/___/___ ☐ Ongoing

Ischaemic heart disease: _____ ☐ Onset date ___/___/___ ☐ Ongoing

Valvular cardiopathy: _____ ☐ Onset date ___/___/___ ☐ Ongoing

Hypertension: _____ ☐ Onset date ___/___/___ ☐ Ongoing

Heart surgery: _____ ☐ Onset date ___/___/___ ☐ Ongoing

Other cardiovascular (CV) disease or CV risk factors:

..... Start date ___/___/___ ☐ Ongoing

..... Start date ___/___/___ ☐ Ongoing

..... Start date ___/___/___ ☐ Ongoing

Other medical history:

..... Start date ___/___/___ ☐ Ongoing

..... Start date ___/___/___ ☐ Ongoing

..... Start date ___/___/___ ☐ Ongoing

Other baseline conditions:

Hepatic impairment ☐ NO ☐ YES: ☐ Mild ☐ Moderate ☐ Severe

If YES, please specify labs values .....

Renal impairment ☐ NO ☐ YES: ☐ Mild ☐ Moderate ☐ Severe

If YES, please specify labs values .....

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Concomitant treatments (including self-medication products):				
Name	Indication	Dosage	Start date	End date
			__/__/__	__/__/__
			__/__/__	__/__/__
			__/__/__	__/__/__
			__/__/__	__/__/__
			__/__/__	__/__/__

Treatment details:				
	Indication	Dosage	Start date	End date
Braftovi			__/__/__	__/__/__
Batch number:				
Mektovi			__/__/__	__/__/__
Batch number:				

Adverse reaction(s):	**Onset date**	**End date**	**Ongoing (Yes/No)**	**Grade NCI CTCAE**
	__/__/__	__/__/__		
	__/__/__	__/__/__		
	__/__/__	__/__/__		
	__/__/__	__/__/__		

Please describe signs and symptoms(s) and provide further details e.g. vital signs, clinical findings, associated events, non-clinical findings (laboratory data, imaging…) confounding factors and corrective therapy

_____
_____
_____
_____
_____
_____
_____
_____

Diagnostic findings: *Please provide details on relevant investigational tests performed*		
Test(s)	**Dates**	**Results and Units**
ECG	___/___/___ ___/___/___	
Echocardiogram	___/___/___ ___/___/___	
Chest CT scan or MRI	___/___/___ ___/___/___	
On-treatment LVEF	___/___/___	
Post-treatment LVEF	___/___/___	
Myocardial scintigraphy	___/___/___	
Cardiac enzymes	___/___/___	
Others: _____	___/___/___	
Others: _____	___/___/___	
Please use additional pages if needed or attach relevant findings (e.g. labs, imaging, pathology report...)		

Seriousness criteria

☐ Death ☐ Disability/invalidity

☐ Life threatening ☐ Congenital anomaly

☐ Hospitalization or prolongation of existing from ___/___/___ to ___/___/___

☐ Other reason – please specify: _____

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Action taken for Braftovi

Did the adverse reaction(s) lead to?

Corrective treatment?	☐ NO	☐ YES	Please specify:
Braftovi discontinuation?	☐ NO	☐ YES	Date of discontinuation: ___/___/___
Dose reduction?	☐ NO	☐ YES	Reduced dose: ____
Dose suspension?	☐ NO	☐ YES	From ___/___/___ to ___/___/___
Was Braftovi resumed?	☐ NO	☐ YES	Date of reintroduction: ___/___/___
Did the adverse reaction reoccur?	☐ NO	☐ YES	Date of recurrence: ___/___/___

Action taken for Mektovi

Did the adverse reaction(s) lead to?

Corrective treatment?	☐ NO	☐ YES	Please specify:.....
Mektovi discontinuation?	☐ NO	☐ YES	Date of discontinuation: ___/___/___
Dose reduction?	☐ NO	☐ YES	Reduced dose: ____
Dose suspension?	☐ NO	☐ YES	From ___/___/___ to ___/___/___
Was Mektovi resumed?	☐ NO	☐ YES	Date of reintroduction: ___/___/___
Did the adverse reaction reoccur?	☐ NO	☐ YES	Date of recurrence: ___/___/___

Patient outcome

☐ Recovered/Resolved	Date of recovery: ___/___/___
☐ Recovering/Resolving	
☐ Not recovered/not resolved	
☐ Recovered/resolved with sequelae	Please specify:.....
☐ Fatal	Date of death: ___/___/___
☐ Unknown	

Reporter's explanation about the causal relationship between the adverse reaction(s) and Braftovi, Mektovi, or both Braftovi and Mektovi:

_____

_____

_____

Has this case been notified to Competent Authorities? No ☐ Yes ☐

Date: _____

Name, qualification and/or stamp Signature:

Thank you for filling out this Pharmacovigilance Form

[1] In European Economic Area (EEA) - INFORMATION FOR THE REPORTER: The data collected about you will be subject to data processing in accordance with the provisions of the General Data Protection Regulation (GDPR) of April 27, 2016. All information and personal data that you share with us via this form will be protected and will remain confidential in accordance with our company policy and the regulation in force. The information you provide will be used for safety monitoring and may be shared with health authorities, the processing of your personal data being necessary for compliance with a legal obligation to which Pierre Fabre is subject. Please note that this personal data will be deleted or anonymized 50 years after marketing authorization withdrawal of our products. You have a right of access, rectification and restriction of processing of your personal data. You can exercise these rights by contacting us at generic email address *(local GDPR contact to be completed)*. You have the right to lodge a complaint with the national supervisory authority in charge of protection of personal data *(name to be completed)*.

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ADVERSE DRUG REACTION COLLECTION FORM - BRAFTOVI AND MEKTOVI COMBINATION - PNEUMONITIS / INTERSTITIAL LUNG DISEASE (ILD)

File n°: |__|__|__|__| - |__|__|__|__|__| *(For department use only - Make no entry in this space)*

Reporter's information[y]:

Name:	❑ Healthcare Professional: ❑ Physician ❑ Pharmacist ❑ Other: _____
Address:	
Tel:	❑ Patient ❑ Other : .....

Patient identification
First Name (first 3 letters): |__|__|__| Last Name (first 2 letters): |__|__|
Date of birth: _____ or Age: _____ Gender: _____ Weight: _____ Height: _____

Medical history:

_____	Start date ___/___/___	❑ Ongoing
_____	Start date ___/___/___	❑ Ongoing
_____	Start date ___/___/___	❑ Ongoing
_____	Start date ___/___/___	❑ Ongoing
_____	Start date ___/___/___	❑ Ongoing

Relevant medical lung disease history:

History of pneumonitis/ILD	❑ Start date ___/___/___	❑ Ongoing
Cause of pneumonitis: _____		
Smoking	❑ Start date ___/___/___	❑ Ongoing
COPD	❑ Start date ___/___/___	❑ Ongoing
Connective tissue disease	❑ Start date ___/___/___	❑ Ongoing
Immunological disease	❑ Please specify: _____	
Other	❑ Please specify: _____	

Previous therapy

Interferon therapy	❑
Amiodarone	❑
Other medications known to cause interstitial lung disease	❑
Radiotherapy	❑ From __/___/___to __/___/___

Dosing regimen: _____ Irradiated areas/organs: _____

Other baseline conditions:
Hepatic impairment ❑ NO ❑ YES - ❑ Mild ❑ Moderate ❑ Severe –
If YES, please specify labs values _____
Renal impairment ❑ NO ❑ YES - ❑ Mild ❑ Moderate ❑ Severe -
If YES, please specify labs values _____
Baseline LVEF: _____ % (Lower Limit of Normal = _____)

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Concomitant treatments (including self-medication products):				
Name	Indication	Dosage	Start date	Ongoing
			__/__/__	
			__/__/__	
			__/__/__	
			__/__/__	

Treatment details:				
	Indication	Dosage	Start date	End date
Braftovi			__/__/__	__/__/__
Batch number:				
Mektovi			__/__/__	__/__/__
Batch number:				

Adverse reaction(s):	**Onset date**	**End date**	**Ongoing? (Yes/No)**	**Grade NCI CTCAE**
	__/__/__	__/__/__		
	__/__/__	__/__/__		
	__/__/__	__/__/__		

Please describe the adverse reaction(s) and provide further details e.g. clinical findings, associated signs and symptoms, non-clinical findings (laboratory, imaging…)

Diagnostic findings: *Please provide details on relevant investigational tests performed*		
Test(s)	**Dates**	**Results and units**
Chest XRay, Chest CT scan, MRI	___/___/___ ___/___/___ ___/___/___	
Bronchoscopy/ Fibroscopy	___/___/___	
Pulmonary function tests, Arterial blood gazes/PO2	___/___/___	
Bronchoalveolar lavage	___/___/___	
Lung biopsy	___/___/___	
Others: Serology of microbial agents (legionella, chlamydiae, mycoplasms)	___/___/___	
Eosinophils count	___/___/___	
Other labs	___/___/___	
Please use additional pages if needed or attach relevant findings (e.g. labs, imaging, pathology report...)		

Seriousness criteria

☐ Death ☐ Disability/invalidity

☐ Life threatening ☐ Congenital anomaly

☐ Hospitalization or prolongation of existing from ___/___/___ to ___/___/___

☐ Other reason, please specify: _____

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Action taken for Braftovi
Did the adverse reaction(s) lead to?

Corrective treatment?	☐ NO	☐ YES	Please specify:
Braftovi discontinuation?	☐ NO	☐ YES	Date of discontinuation: ___/___/___
Dose reduction?	☐ NO	☐ YES	Reduced dose: ____
Dose suspension?	☐ NO	☐ YES	From ___/___/___ to ___/___/___
Was Braftovi resumed?	☐ NO	☐ YES	Date of reintroduction: ___/___/___
Did the adverse reaction reoccur?	☐ NO	☐ YES	Date of recurrence: ___/___/___

Action taken for Mektovi
Did the adverse reaction(s) lead to?

Corrective treatment?	☐ NO	☐ YES	Please specify: _____
Mektovi discontinuation?	☐ NO	☐ YES	Date of discontinuation: ___/___/___
Dose reduction?	☐ NO	☐ YES	Reduced dose: ____
Dose suspension?	☐ NO	☐ YES	From ___/___/___ to ___/___/___
Was Mektovi resumed?	☐ NO	☐ YES	Date of reintroduction: ___/___/___
Did the adverse reaction reoccur?	☐ NO	☐ YES	Date of recurrence: ___/___/___

Patient outcome

☐ Recovered/Resolved	Date of recovery: ___/___/___	☐ Unknown
☐ Recovering/Resolving		
☐ Not recovered/not resolved		
☐ Recovered/resolved with sequelae	Please specify: _____	
☐ Fatal	Date of death: ___/___/___	

Reporter's explanation about the causal relationship between the adverse reaction(s) and Braftovi, Mektovi, or both Braftovi and Mektovi:

_____

_____

_____

Has this case been notified to Competent Authorities? : No ☐ Yes ☐

Date: _____
Name, qualification and/or stamp

Signature:

Thank you for filling out this Pharmacovigilance Form

[1] In European Economic Area (EEA) - INFORMATION FOR THE REPORTER: The data collected about you will be subject to data processing in accordance with the provisions of the General Data Protection Regulation (GDPR) of April 27, 2016. All information and personal data that you share with us via this form will be protected and will remain confidential in accordance with our company policy and the regulation in force. The information you provide will be used for safety monitoring and may be shared with health authorities, the processing of your personal data being necessary for compliance with a legal obligation to which Pierre Fabre is subject. Please note that this personal data will be deleted or anonymized 50 years after marketing authorization withdrawal of our products. You have a right of access, rectification and restriction of processing of your personal data. You can exercise these rights by contacting us at generic email address *(local GDPR contact to be completed)*. You have the right to lodge a complaint with the national supervisory authority in charge of protection of personal data *(name to be completed)*.

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ADVERSE DRUG REACTION COLLECTION FORM - BRAFTOVI AND MEKTOVI COMBINATION - SERIOUS HEMORRHAGE

File n°: |__|__|__|__| - |__|__|__|__|__| *(For department use only - Make no entry in this space)*

Reporter's information[6]:

Name: .....
Address: .....
Tel: .....

❑ Healthcare Professional: ❑ Physician ❑ Pharmacist ❑ Other: _____
❑ Patient
❑ Other: _____

Patient identification
First Name (first 3 letters): |__|__|__| Last Name (first 2 letters): |__|__|
Date of birth: _____ or Age: _____ Gender: _____ Weight: _____ Height: _____

Medical history (personal or family):

_____ Start date ___/___/___ ❑ Ongoing
_____ Start date ___/___/___ ❑ Ongoing
_____ Start date ___/___/___ ❑ Ongoing
_____ Start date ___/___/___ ❑ Ongoing
_____ Start date ___/___/___ ❑ Ongoing

Relevant history of haemorrhage/bleeding disorders:
Prior haemorrhage/bleeding episode(s): ❑ NO ❑ YES
Start date ___/___/__ ❑ Ongoing
Site: _____ Etiology: _____
Hepatic impairment: ❑ NO ❑ YES ❑ Mild ❑ Moderate ❑ Severe
If YES, please specify labs values: _____

Decreased platelet count ❑ NO ❑ YES Start date ___/___/___ ❑ Ongoing
Anemia ❑ NO ❑ YES Start date ___/___/___ ❑ Ongoing
Coagulation factors abnormal: ❑ NO ❑ YES Start date ___/___/___ ❑ Ongoing
Please specify: _____
History of trauma or fall: ❑ NO ❑ YES Start date ___/___/___ ❑ Ongoing
Please specify: _____
Chronic alcohol intake ❑ NO ❑ YES Start date ___/___/___ ❑ Ongoing
Previous drug-induced bleeding: ❑ NO ❑ YES Start date ___/___/___ ❑ Ongoing
Please specify: _____
Anticoagulant or antiplatelet therapy: ❑ NO ❑ YES Start date ___/___/___ ❑ Ongoing
Please specify: _____

Other baseline conditions:
Renal impairment ❑ NO ❑ YES - ❑ Mild ❑ Moderate ❑ Severe
If YES, please specify labs values _____
Baseline LVEF: _____ % (Lower Limit of Normal = _____)

Concomitant treatments (including self-medication products):

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Name	Indication	Dosage	Start date	Ongoing
			__/__/__	
			__/__/__	
			__/__/__	
			__/__/__	

Treatment details:				
	Indication	Dosage	Start date	End date
Braftovi			__/__/__	__/__/__
Batch number:				
Mektovi			__/__/__	__/__/__
Batch number:				

Adverse reaction(s):	Onset date	End date	Ongoing? (Yes/No)	Grade NCI CTCAE
	__/__/__	__/__/__		
	__/__/__	__/__/__		
	__/__/__	__/__/__		

Please describe the adverse reaction(s) and provide further details e.g. clinical findings, associated signs and symptoms, non-clinical findings (laboratory, imaging...)

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Diagnostic findings: *Please provide details on relevant investigational tests performed*			
	Date	Values and units	Lower Limit of Normal
Hemoglobin	___/___/___		
Platelet count	___/___/___		
INR or PT or Prothrombin time Coagulation factors	__ /__/___ ___/___/___ ___/___/___		
Other labs Bilirubin total ALT AST ALP Albumin	 ___/___/___ ___/___/___ ___/___/___ ___/___/___ ___/___/___		
Imaging (Ultrasound, TDM, MRI)	___/___/___ ___/___/___		
Other	___/___/___		

Seriousness criteria

☐ Death ☐ Disability/invalidity

☐ Life threatening ☐ Congenital anomaly

☐ Hospitalization or prolongation of existing from ___/___/___ to ___/___/___

☐ Other reason – please specify: _____

Action taken for Braftovi

Did the adverse reaction(s) lead to?

Corrective treatment?	☐ NO	☐ YES	Please specify: _____
Braftovi discontinuation?	☐ NO	☐ YES	Date of discontinuation: ___/___/___
Dose reduction?	☐ NO	☐ YES	Reduced dose: ____
Dose suspension?	☐ NO	☐ YES	From ___/___/___ to ___/___/___
Was Braftovi resumed?	☐ NO	☐ YES	Date of reintroduction: ___/___/___
Did the adverse reaction reoccur?	☐ NO	☐ YES	Date of recurrence: ___/___/___

Action taken for Mektovi

Did the adverse reaction(s) lead to?

Corrective treatment?	☐ NO	☐ YES	Please specify: _____
Mektovi discontinuation?	☐ NO	☐ YES	Date of discontinuation: ___/___/___
Dose reduction?	☐ NO	☐ YES	Reduced dose: ____
Dose suspension?	☐ NO	☐ YES	From ___/___/___ to ___/___/___
Was Mektovi resumed?	☐ NO	☐ YES	Date of reintroduction: ___/___/___
Did the adverse reaction reoccur?	☐ NO	☐ YES	Date of recurrence: ___/___/___

Patient outcome

☐ Recovered/Resolved	Date of recovery: ___/___/___
☐ Recovering/Resolving	
☐ Not recovered/not resolved	
☐ Recovered/resolved with sequelae	Please specify: _____
☐ Fatal	Date of death: ___/___/___
☐ Unknown	

Reporter's explanation about the causal relationship between the adverse reaction(s) and Braftovi, Mektovi, or both Braftovi and Mektovi:

_____

_____

_____

_____

Has this case been notified to Competent Authorities? No ☐ Yes ☐

Date: _____

Name, qualification and/or stamp

Signature:

Thank you for filling out this Pharmacovigilance Form

[1] In European Economic Area (EEA) - INFORMATION FOR THE REPORTER: The data collected about you will be subject to data processing in accordance with the provisions of the General Data Protection Regulation (GDPR) of April 27, 2016. All information and personal data that you share with us via this form will be protected and will remain confidential in accordance with our company policy and the regulation in force. The information you provide will be used for safety monitoring and may be shared with health authorities, the processing of your personal data being necessary for compliance with a legal obligation to which Pierre Fabre is subject. Please note that this personal data will be deleted or anonymized 50 years after marketing authorization withdrawal of our products. You have a right of access, rectification and restriction of processing of your personal data. You can exercise these rights by contacting us at generic email address *(local GDPR contact to be completed)*. You have the right to lodge a complaint with the national supervisory authority in charge of protection of personal data *(name to be completed)*.

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Issuing Department: CORPORATE VIGILANCES		

ADVERSE DRUG REACTION COLLECTION FORM - BRAFTOVI AND MEKTOVI COMBINATION - HEPATIC REACTIONS

File n°: |__|__|__|__| - |__|__|__|__|__| *(For department use only - Make no entry in this space)*

Reporter's information[(f)]:

Name: .....
Address: .....
Tel: .....

❑ Healthcare Professional: ❑ Physician ❑ Pharmacist ❑ Other: _____
❑ Patient
❑ Other : .....

Patient identification
First Name (first 3 letters): |__|__|__| Last Name (first 2 letters): |__|__|
Date of birth: _____ or Age: _____ Gender: _____Weight: _____ Height: _____

Medical history:

_____ Start date ___/___/___ ☐ Ongoing
_____ Start date ___/___/___ ☐ Ongoing
_____ Start date ___/___/___ ☐ Ongoing
_____ Start date ___/___/___ ☐ Ongoing

Relevant history of hepatic conditions:

Hepatic impairment before treatment with Braftovi and/or Mektovi:
☐ NO ☐ YES: ☐ Mild ☐ Moderate ☐ Severe
If YES, please specify labs values _____

History of Hepatitis ☐ Start date ___/___/___ ☐ Ongoing
Cause: _____

History of cirrhosis ☐ Start date ___/___/___ ☐ Ongoing

History of other liver problem ☐ Start date ___/___/___ ☐ Ongoing
Please specify: _____

Chronic alcohol intake ☐ Start date ___/___/___ ☐ Ongoing
Malnutrition ☐ Start date ___/___/___ ☐ Ongoing
Other ☐ Please specify: _____

Previous Drug-induced liver injury

_____ ☐ From __/___/___to __/___/___
_____ ☐ From __/___/___to __/___/___
_____ ☐ From __/___/___to __/___/___

Other baseline conditions:
Renal impairment ☐ NO ☐ YES : ☐ Mild ☐ Moderate ☐ Severe
If YES, please specify labs values .....
Baseline LVEF: _____% (Lower Limit Normal = _____)

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Concomitant treatments (including self-medication products):				
Name	Indication	Dosage	Start date	Ongoing
			__/__/__	
			__/__/__	
			__/__/__	
			__/__/__	

Treatment details:				
	Indication	Dosage	Start date	End date
Braftovi			__/__/__	__/__/__
Batch number:				
Mektovi			__/__/__	__/__/__
Batch number:				

Adverse reaction(s):	**Onset date**	**End date**	**Ongoing? (Yes/No)**	**Grade NCI CTCAE**
	__/__/__	__/__/__		
	__/__/__	__/__/__		
	__/__/__	__/__/__		

Please describe the adverse reaction(s) and provide further details e.g., clinical findings, associated signs and symptoms, non-clinical findings (laboratory, imaging...)

Diagnostic findings: *Please provide details on relevant investigational tests performed*		
Test(s)	**Dates**	**Results and units**
AST before treatment	__/__/___ __/__/___ __/__/___	
AST during treatment	__/__/__ __/__/___ __/__/___	
ALT before treatment	__/__/___ __/__/___ __/__/___	
ALT during treatment	__/__/___ __/__/___ __/__/___	
ALP before treatment	__/__/___ __/__/___ __/__/___	
ALP during treatment	__/__/___ __/__/___ __/__/___	
GGT before treatment	__/__/___	
GGT during treatment	__/__/___ __/__/___ __/__/___	
Total bilirubin before treatment	__/__/___	
Total bilirubin during treatment	__/__/___ __/__/___ __/__/___	
Platelet count before treatment	__/__/___	
Platelet count during treatment	__/__/___	
Kidney biopsy	__/__/___	
Viral infection (A, B, C, D, E virus/ EBV / CMV)	__/__/___	
INR / PT	__/__/___	
Other labs	__/__/___	
Please use additional pages if needed or attach relevant findings (e.g. labs, imaging, pathology report...)		

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Seriousness criteria

☐ Death ☐ Disability/invalidity
☐ Life threatening ☐ Congenital anomaly
☐ Hospitalization or prolongation of existing from ___/___/___ to ___/___/___
☐ Other reason – please specify: _____

Action taken for Braftovi

Did the adverse reaction(s) lead to?

Corrective treatment?	☐ NO	☐ YES	Please specify: _____
Braftovi discontinuation?	☐ NO	☐ YES	Date of discontinuation: ___/___/___
Dose reduction?	☐ NO	☐ YES	Reduced dose: ____
Dose suspension?	☐ NO	☐ YES	From ___/___/___ to ___/___/___
Was Braftovi resumed?	☐ NO	☐ YES	Date of reintroduction: ___/___/___
Did the adverse reaction reoccur?	☐ NO	☐ YES	Date of recurrence: ___/___/___

Action taken for Mektovi

Did the adverse reaction(s) lead to?

Corrective treatment?	☐ NO	☐ YES	Please specify: _____
Mektovi discontinuation?	☐ NO	☐ YES	Date of discontinuation: ___/___/___
Dose reduction?	☐ NO	☐ YES	Reduced dose: ____
Dose suspension?	☐ NO	☐ YES	From ___/___/___ to ___/___/___
Was Mektovi resumed?	☐ NO	☐ YES	Date of reintroduction: ___/___/___
Did the adverse reaction reoccur?	☐ NO	☐ YES	Date of recurrence: ___/___/___

Patient outcome

☐ Recovered/Resolved — Date of recovery: ___/___/___
☐ Recovering/Resolving
☐ Not recovered/not resolved
☐ Recovered/resolved with sequelae — Please specify: _____
☐ Fatal — Date of death: ___/___/___
☐ Unknown

Reporter's explanation about the causal relationship between the adverse reaction(s) and Braftovi, Mektovi, or both Braftovi and Mektovi:

_____
_____
_____

Has this case been notified to Competent Authorities? No ☐ Yes ☐

Date: _____
Name, qualification and/or stamp Signature:

Thank you for filling out this Pharmacovigilance Form

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Annex 6 - Details of proposed additional risk minimisation activities

Not applicable.

There are no proposed additional risk minimisation activities.