EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 February 2017
EMA/240244/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mekinist	trametinib
Tafinlar	dabrafenib

Procedure No. EMEA/H/C/WS/0996

Note

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

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List of abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BCC	Basel cell carcinoma
bid	Bis in die; twice daily
BRAF	Human gene that makes a protein called B-Raf (regulated signal transduction serine/threonine-specific protein kinase)
CTCAE	Common Terminology Criteria for Adverse Events
CuSCC	Cutaneous squamous cell carcinoma
DCR	Disease control rate
DoR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group Performance Score
EGFR	Epidermal growth factor receptor
EML4	Echinoderm microtubule-associated protein-like 4
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
HPMC	Hydroxypropyl methylcellulose
HR	Hazard ratio
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFCT	Intergroupe Francophone de Cancérologie Thoracique
IRC	Independent Review Committee
MAPK	Mitogen-activated protein kinases
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase kinase
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
RECIST	Response Evaluation Criteria In Solid Tumors
ROS1	ROS proto-oncogene receptor 1 tyrosine kinase
SAE	Serious adverse event
SOC	System organ class

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 27 July 2016 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

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

Extension of indication to include the combination treatment with trametinib and dabrafenib of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the Mekinist and Tafinlar SmPC are updated. The Package Leaflet and RMP are updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to align the SmPCs of Mekinist and Tafinlar. Furthermore, the Product Information is brought in line with the latest QRD template version 10.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decisions P/0024/2016 for Mekinist and P/0022/2016 for Tafinlar on the agreement of a paediatric investigation plan (PIP) and CW/1/20144 on the granting of a class waiver.

At the time of submission of the application, the PIP P/0024/2016 for Mekinist and P/0022/2016 for Tafinlar were not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP for the WS procedure were:

Rapporteur: Filip Josephson Co-Rapporteur: Paula Boudewina van Hennik

Timetable	Actual dates
Submission date	27 July 2016
Start of procedure:	13 August 2016
CHMP Lead WS Co-Rapporteur Assessment Report	7 October 2016
CHMP/PRAC Lead WS Rapporteur Assessment Report	10 October 2016
PRAC members comments	19 October 2016
Updated PRAC Rapporteur Assessment Report	20 October 2016
PRAC Outcome	27 October 2016
CHMP members comments	31 October 2016
Updated CHMP/PRAC Lead WS Rapporteurs Joint Assessment Report	3 November 2016
Request for supplementary information (RSI)	10 November 2016
WSA's responses submitted to the CHMP on:	23 December 2017
CHMP/PRAC Rapporteurs Joint Assessment Report on the WSA's responses	25 January 2017
PRAC members comments	1 February 2017
PRAC Outcome	9 February 2016
CHMP members comments	13 February 2017
Updated CHMP/PRAC Lead WS Rapporteur Assessment Report on the WSA's responses	17 February 2017
Opinion	23 February 2017

2. Scientific discussion

2.1. Introduction

In the European Union (EU), lung cancer is estimated to be the leading cause of cancer death with an estimated 185,000 deaths in men and 82,000 deaths in women in 2012. Besides this, lung cancer is the fourth most common cancer in EU, with 214,000 cases in men and 99,000 cases in women in 2012 (GLOBOCAN, 2012).

The two most prevalent sub-types of lung cancer are small cell lung cancer and NSCLC. Approximately 85% of all lung cancers are NSCLC, which is frequently further subdivided into non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, and other cell types) and squamous cell (epidermoid) carcinoma (Brambilla et al, 2014 and Schrump DS et al NSCLC; Principles and Practice of Oncology. 9th Edition. 2011).

For the majority of patients, NSCLC is diagnosed at an advanced stage with an overall poor prognosis. The overall survival (OS) for metastatic NSCLC is dismal with 5-year survival of <5% (Lindsey A. et al, 2016).

According to the ESMO Clinical Practice Guidelines for metastatic NSCLC (Novello S. et al, 2016), in the absence of driver mutations first-line platinum-based doublet chemotherapy (four with a maximum of six cycles) is recommended in patients with good performance status, based on the observed prolonged survival and improved quality of life (QoL). A comparable efficacy has been observed with several regimens including cisplatin and carboplatin combinations with gemcitabine, paclitaxel and docetaxel (Schiller JH. et al, 2002). The addition of bevacizumab to platinum-based backbone regimen improved OS in non-squamous NSCLC patients with ECOG PS 0-1 (Sandler A. et al, 2006).

Recently, the anti-PD1 anti-body pembrolizumab has been approved as first line treatment in NSCLC patients whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS).

In case of epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) gene rearrangements, approved target therapy agents are available.

Treatment options currently available for patients with NSCLC who have experienced disease progression after first-line platinum combination chemotherapy depend essentially on tumour histology and the presence of specific biomarkers in tumour tissue. The cytostatic anticancer drug docetaxel, alone or in combination with ramucirumab and the EGFR TKI erlotinib are the only palliative treatment options available as monotherapy for an unselected NSCLC population (i.e., independent of tumour histology). In NSCLC patients with other than predominantly squamous cell histology, pemetrexed is also available as second line or as maintenance therapy after first line platinum-pemetrexed combination. In NSCLC patients with adenocarcinoma histology nintedatinb (a VEGFR 1-3, FGFR 1-3 and PDGFRα, β tyrosine kinase inhibitor) has been approved in combination with docetaxel as second line therapy. The anti-PD1 anti-body nivolumab has been approved as second line therapy.

Despite the development of new anti-cancer treatments, advanced NSCLC remains incurable. The subgroup of patients with non-squamous NSCLC who benefit most from systemic treatment are those who receive targeted therapies based on the presence of a specific actionable molecular aberration (Barlesi et al 2016).

BRAF mutations in NSCLC

Constitutively activating mutations in the BRAF gene, first described in melanoma and then in lung cancer in 2002 (Davies et al 2002, Naoki et al 2002), appear to drive growth and survival of cancer cells that harbour them and are extremely sensitive to selective BRAF inhibitor therapy across multiple tumour types (Wan et al 2004). BRAF is a serine/threonine kinase that lies downstream of RAS in the RAS-RAF-MEK-ERK signalling pathway, also known as the mitogen-activated-protein-kinase and is a key molecular cascade that regulates cell growth, proliferation, and differentiation. The vast majority of BRAF mutations are V600 missense mutations, which lead to constitutive activation of BRAF kinase activity, resulting in MAPK activation and constant transduction of cellular growth and inhibition of pro-apoptotic signals that results in a malignant phenotype.

BRAF V600 mutations are most commonly seen in melanoma, but are also identified in other cancers (Davies et al 2002). BRAF mutations are observed in approximately 2% of NSCLC and occur most frequently in adenocarcinomas (Pratilas et al 2008, Cardarella et al 2013; Marchetti et al 2011). In contrast to melanoma, in NSCLC there is a large number of other activating BRAF mutations on exon 15 and 11 (Tissot, et al 2016). BRAF V600E occurs in approximately half of all BRAF mutations in NSCLC. In addition to V600E, there are other BRAF V600 mutations, such as V600K, that also lead to constitutive activation and are sensitive to BRAF inhibitors. Preclinical data in mice suggest a potential oncogenic role in the development of adenocarcinoma of the lung for BRAF V600 mutations (Nuyen-Ngoc et al 2015). Non-V600 BRAF mutations often occur in the phosphate binding loop and tumours harbouring those mutations are not sensitive to BRAF inhibitors.

The natural history of NSCLC harbouring BRAFV600 mutations is not completely clear due to contrasting results in the literature. Indeed BRAF V600E mutations in NSCLC have been associated with shorter overall survival (OS) and lower response rates to platinum-based chemotherapy than in patients with wild-type BRAF (Marchetti et al 2011, Cardarella et al 2013, Kris et al 2014). However, a report from Lung Cancer Mutation Consortium indicated that there was no difference in overall survival with outcomes similar to the general NSCLC population (Villaruz et al 2015), whereas in the Intergroupe Francophone de Cancerologie Thoracique (IFCT) database BRAF V600E mutations were associated with a slightly longer survival rates when compared with BRAF wildtype patients.

Importantly, BRAF mutations and other oncogenic drivers, including EGFR and KRAS mutations as well as ALK rearrangements, are typically mutually exclusive; this is consistent with the notion that BRAF mutation defines a unique molecular subset of patients with NSCLC who may benefit from treatment that inhibits the MAPK pathway.

Dabrafenib and trametinib are licensed for the treatment of BRAF V600 driven malignant melanoma and target two different kinases in the RAS/RAF/MEK/ERK pathway. Dabrafenib is a selective inhibitor of BRAF kinase activity which competes for the ATP (adenosine triphosphate) binding site in the kinase domain. Trametinib is a reversible and selective allosteric inhibitor of the mitogen-activated extracellular signal-regulated kinase (MEK)1 and MEK2 and inhibits its kinase activity.

The current application concerns their combined use in the treatment of BRAF V600 mutation positive NSCLC. BRAF V600 mutations have been identified as driving mutations in about 2% of patients with NSCLC.

2.2. Non-clinical aspects

2.2.1. Introduction

The MAH has submitted 3 PD/PK in vitro and in vivo studies relevant to the new indication.

2.2.2. Pharmacology

Primary pharmacodynamic studies

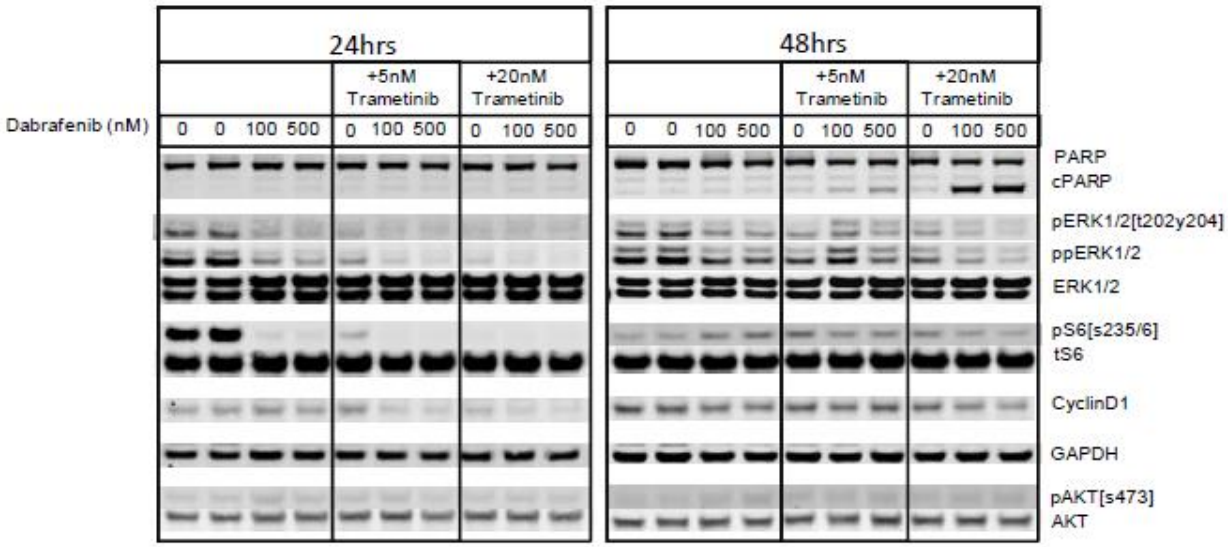
In vitro assessment of sensitivity of several BRAF V600E-mutant lung carcinoma-derived cell line models to combined dabrafenib and trametinib (Study 2013N169244_00)

Method

The effect of dabrafenib and trametinib on the MAPK and PI3K/AKT pathways was characterized by Western blot analyses in MV522 and A375 cell lines after treatment for 24 hours, 48 hours, or 72 hours.

Results

The combination of dabrafenib (10 nM, 100 nM, or 500 nM) and trametinib (5 nM or 20 nM) was more effective at inhibiting the MAPK pathway than both single agents. Dabrafenib at either 100 nM or 500 nM in combination with 5 nM trametinib showed similar effects. Cyclin D1 was reduced by the combination of dabrafenib and trametinib, but not by either single agent after 24 and 48 hours of treatment in MV522 cells. The level of phosphorylated AKT was low with and without treatment of dabrafenib and trametinib. Apoptosis measured by cleaved PARP was observed in $BRAF^{V600E}$ MV522 cells after treatment with 5 nM trametinib, 10 nM or 100 nM dabrafenib for 48 hours or 72 hours. Apoptosis was enhanced by the combination of dabrafenib and trametinib (Figure 1).



MAPK and PI3K/AKT pathway western blot analysis after treatment of $BRAF^{V600E}$ lung line MV522 with dabrafenib, trametinib or in combination

Both single agent and combined trametinib and dabrafenib inhibited the proliferation of the BRAFV600E cell line MV522 with single digit nM IC50 values, similar to what was observed in the BRAFV600E A-375 melanoma-derived cell line.

2.2.3. Pharmacokinetics

Exposure and distribution of Dabrafenib and its metabolites: GSK2298683 (M4), GSK2285403 (M7) and GSK2167542 (M8), in brain, lung, liver, kidney, and tumour tissues following 22 day repeat oral administration of GSK2118436A in female mice bearing A375P F11s tumour xenografts using MALDI-IMS and LC-MS (study 2001N127421_00)

Method

The primary objective of this investigative study was to assess the tissue distribution of Dabrafenib and its main metabolites GSK2167542 (M8), GSK2285403 (M7) and GSK2298683 (M4) in brain, lung, liver, kidney, and tumour tissues from female mice bearing tumour xenografts at selective time points (0, 2, 6 and 12h post terminal dose) following repeat oral administration of GSK2118436A for 22 days at 30 mg/kg/day. The tissue distribution of Dabrafenib and metabolites M4, M7, and M8 was examined by matrix-assisted laser desorption/ionization (MALDI) imaging mass spectrometry (IMS). Tissue

homogenate concentrations were determined by LC-MS.

Results

Extensive conversion (~90%) of M4 to M8 through decarboxylation occurs during the MALDI process. The LC-MS quantification data showed that, in general, M4 was present in markedly higher concentrations than M8 in the tissues analysed. Given that the conversion of M4 to M8 was shown to be consistent across a large range of concentrations, the signal for M8 detected by MALDI IMS was used as a surrogate for M4, and referred to as M4*.

In the liver, at 2h and 6h, MALDI IMS showed that Dabrafenib, M7, and M4* shared a similar homogeneous multi-zonal distribution throughout the tissues with M4* being detected with highest intensity. At 12h, only M4* is still present at detectable levels. No drug-related material was detected in the liver by MALDI IMS at the 0h timepoint. In the kidney, M4* appeared to localize predominantly to the cortico-medullary junction, with highest intensity at the 2h timepoint and markedly lower intensities at 6h and 12h. Dabrafenib and M7 were detected at low levels in the cortex at 2h and 6h but were not detected in the 12h kidney tissues. No drug-related material was detected by MALDI IMS in the 0h timepoint kidney tissues. In the xenograft tumour tissues, M4* was detected at high levels in both 2h and 6h tissues. Low levels of Dabrafenib and M7 were also detected in the tumour tissues at these timepoints. Xenograft tumour tissues from the 0h and 12h timepoints were not analysed by MALDI IMS.

Dabrafenib and its metabolites M4, M7 and M8 were quantified in brain, lung, liver, kidney, and tumour tissue homogenates from female mice using LC-MS to provide context for the IMS measurements. In general, the LC-MS quantification results were in good agreement with the MALDI IMS results. In the liver and kidney, Dabrafenib, M7, M4, and M8 were quantified at the 2, 6, and 12h timepoints but not the 0h. In the xenograft tumour tissues, Dabrafenib and the three metabolites were quantified in the 2, 6, and 12h tissues and Dabrafenib, M7, and M8 were also quantified at the 0h timepoint. In all tissues examined with the exception of the 0h tumour tissues, M4 was detected at the highest concentrations, and the highest overall levels of M4 were detected in liver, followed by kidney and tumour. Low levels of Dabrafenib, M7, and M8 were observed in the liver, tumour, and kidney. Low levels of M4 were also detected in the Group 2 and 3 brain tissues; however, these results are likely due to blood contamination.

Investigation into the distribution of Dabrafenib and its metabolites GSK2167542 (M8), GSK2285403 (M7) and GSK2298683 (M4), in brain, lung, liver and kidney following repeat oral administration of GSK2118436B to mice for 2 weeks as part of a 26 week oral toxicity study (study 2014N224534_00)

Method

The primary objective of this study was to assess the tissue distribution of Dabrafenib and its main metabolites GSK2167542 (M8), GSK2285403 (M7) and GSK2298683 (M4) in brain, lung, liver and kidney following repeat oral administration at a target dose of 150 mg/kg/day, of GSK2118436B to male and female mice for 2 weeks. Dosing was conducted as part of a 26 week oral toxicity study.

Results

In the lung, unchanged parent compound, Dabrafenib, and two metabolites M7 and M8 had similar distribution within the tissue, with drug-related material being primarily co-located in the blood vessels and supportive interstitial areas. This distribution is supported by the LC-MS data where the concentration of drug related material is much lower in the lung homogenate than in plasma, suggesting that these values may be due to the presence of residual blood, rather than penetration of the drug into the tissue compartment itself. M4 was not detected in the lung directly by IMS but was observed at a higher concentration than M8 in the LC-MS analyses of tissue homogenate.

2.2.4. Ecotoxicity/environmental risk assessment

Trametinib is an orally bioavailable, reversible, highly selective, allosteric inhibitor of MEK1) and MEK2. Dabrafenib is an orally bioavailable inhibitor of B-Raf (BRAF) protein with potential antineoplastic activity. In the current type II variation application, Novartis is seeking approval for the combination of trametinib and dabrafenib in the treatment of adult patients with advanced NSCLC with a BRAF V600 mutation.

Phase I

Accounting for the 5-year survival of patients diagnosed with NSCLC, the estimated 5-year partial prevalence of NSCLC show that 318,611 individuals diagnosed with NSCLC within the previous 5 years were alive in 2012 in the targeted European region. The corresponding prevalence proportion was 6.2 per 10,000. This 5-year prevalence estimate is likely to represent the upper range of the prevalence of NSCLC in the EU region of interest (EUCAN; Pagano et al 2010).

Compared to melanoma, the frequency of BRAF-mutations is very rare in NSCLC and can be detected in only 1-2 of 100 cases of NSCLC. Furthermore, only approximately half of them harbour the activating V600 mutation (Kris et al 2014; Nguyen-Ngoc et al 2015).

Using this information to refine the prevalence derived above for NSCLC, (i.e. a maximum of 2% of the 6.2 in 10'000 NSCLC patients have mutated BRAF V600), results in a prevalence of BRAF V600 mutated NSCLC of 0.124 in 10'000.

The tables summarising the main study results for dabrafenib and trametinib have been updated.

Table 1. Summary of main study results for dabrafenib

Substance (INN/Invented Name): dabrafenib / Rafinlar			
CAS-number (if available): 1195768-06-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log Dow (pH 7) = 3.384	Potential PBT (Y/N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.384	not B
	BCF	<10	
Persistence	DT50 or ready biodegradability		
Toxicity	NOEC or CMR		
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$	1.5 (default) 0.36186 (refined based on prevalence)	µg/L	> 0.01 threshold
Other concerns (e.g. chemical class)			No
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OPPTs 835.1110	K_{oc} =2460	
Ready Biodegradability Test	OECD 301	Not inherently biodegradable Ultimate biodegradation (DOC) = 0% Primary degradation = 81%	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ whole\ system}$ =162-307 days	

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	NOEC	0.22	mg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.0583	mg/L	No toxicity observed but upper limit of test limited by low water solubility
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	1.47	mg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	312.5	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	**0.01 mg/L** BCFss = 4.38 BCFk = 3.46 Depuration: DT_{50} = 0.71 days DT_{95} = 3.06 days **0.1 mg/L** BCFss = 3.98 BCFk = 3.40 Depuration: DT_{50} = 0.74 days DT_{95} = 3.19 days			*Oncorhynchus mykiss*
Sediment dwelling organism, water chironomid toxicity test	OECD 218	NOEC	64	mg/kg	*Chironomus riparius*

Table 2. Summary of main study results for trametinib

Substance (INN/Invented Name): Trametinib / Tafinlar			
CAS-number (if available): 871700-17-3 or 1187431-43-1 (trametinib dimethyl sulfoxide)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential – log K_{ow}	OECD107	log K_{OW} = 4.04	not B
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	log K_{OW} = 4.04	not B
	BCF	-	
Persistence	DT50 or ready biodegradability	-	
Toxicity	NOEC or CMR	-	
PBT-statement	trametinib is not PBT, nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined F_{pen} (based on prevalence)	0.00241	µg/L	< 0.01 threshold
Other concerns (e.g. chemical class)	not investigated		

Trametinib is not considered to be PBT, nor vPvB.

The PECsurfacewater for trametinib is 2.41 ng/L, which is below the action limit of 0.01 µg/L. Trametinib is not expected to pose a risk to the environment.

2.3. Discussion on non-clinical aspects

The in vitro studies looking at both anti-proliferative effects and changes in signalling, apoptosis and cell cycle biomarkers indicate that a BRAFV600E NSCLC model behaves very similarly to a BRAFV600E melanoma model when treated with single agent and with combined dabrafenib and trametinib. The data presented are consistent with dual inhibition of the BRAF and MEK signaling pathways having the potential to benefit BRAF V600E mutation positive lung cancer.

Dabrafenib and its three metabolites were well distributed into tumours with M4 being the most abundant of the dabrafenib-related components (maximum concentration (C_{max}) ~7 times higher than that of dabrafenib). C_{max} of dabrafenib, M4, M7 and M8 in tumours were between 0.3 and 1.8 times those in plasma (0.5 times for dabrafenib). The concentrations in the lung were low (generally 0.1 to 0.2 times those in plasma at 0.5 h post-final dose in normal mice; less in tumour-bearing mice at later times after last dose).

The studies presented as part of the ERA have already been assessed in relation to the first MAA indication (melanoma) and the addition of a new indication (increased usage) does not change the conclusion that neither dabrafenib nor trametinib are expected to pose a significant risk to the environment.

For trametinib the PEC remains below the trigger value of 0.01 µg/L and a Phase II assessment is not required.

For dabrafenib, the Phase II Tier A risk assessment suggests no risk for surface waters, groundwater and microorganisms in sewage treatment plant activated sludge, with the highest risk ratio of 0.000244 found for surface water. Adsorption potential of dabrafenib observed in batch equilibrium studies with sludge remained well below the trigger level for a terrestrial assessment. The study on transformation in water-sediment study showed significant shifting of dabrafenib into sediment compartments therefore leading to a Tier B risk assessment for sediments.

Dabrafenib shows modest toxicity to the sediment-dwelling larvae of Chironomus riparius and the subsequent risk assessment for sediment compartments resulted in a risk ratio of 0.0024 indicating no risk of this API for sediments.

In a bioconcentration study in fish, dabrafenib showed very low bioaccumulation potential with a maximum BCF_{ss} of 4.38.

Considering the above data, dabrafenib is not expected to pose a significant risk to the environment.

2.3.1. Conclusion on the non-clinical aspects

The non-clinical data submitted is considered acceptable. Dabrafenib and/or trametinib is not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

This application for dabrafenib in combination with trametinib for the treatment of BRAF V600 mutation-positive advanced NSCLC is based on the results of a single Phase II BRF113928 study at the time of initial NSCLC application (data cut-off 7-Oct-2015).

Purpose	Details	Treatment dose regimen	Number of patients	Status
Registration study	BRF113928: Phase II, open-label, multi-center study evaluating efficacy/tolerability of dabrafenib/trametinib vs. dabrafenib monotherapy in patients with BRAF V600E mutation-positive metastatic (stage IV) NSCLC	Cohort A: dabrafenib 150 mg bid	84 total; 78 2L+, 6 1L[b]	Ongoing
		Cohort B: dabrafenib 150 mg bid + trametinib 2 mg once daily	59 total; 57 2L+, 2 1L[a, b]	
		Cohort C: dabrafenib 150 mg bid + trametinib 2 mg once daily	23 1L[b]	

2L+ = 2nd line plus; 1L = 1st line.

a: Two patients who had not received any prior anti-cancer therapy for metastatic disease were enrolled in Cohort B, and were captured as protocol deviations.
b: Data cut-off: 07-Oct-2015

2.4.2. Pharmacokinetics

2.4.2.1. Methods

Analytical methods

Plasma samples from study BRF113928 Cohort A (dabrafenib and metabolite) were analysed at Aptuit, Verona, Italy using two separate validated assays; one assay (Method VPT0224) to measure dabrafenib and its two metabolites hydroxy-dabrafenib (M7) and desmethyl-dabrafenib (M8), and one (Method VPT0225) for carboxy-dabrafenib (M4). These assays were previously used and discussed in the original MAA assessment for dabrafenib. The validation report was since updated with more long-term stability data. Cohort B and Cohort C samples from study BRF113928 were assayed at Covance, Madison, Wisconsin (WI). An assay was validated to simultaneously measure dabrafenib, hydroxy-dabrafenib (M7), desmethyl-dabrafenib (M8), and trametinib in human plasma (Method GGGHPP) and a separate assay was validated to measure carboxy-dabrafenib (M4) in human plasma (Method G83HPP). As sample analysis was performed at two different bioanalytical sites, cross validation was performed between these sites.

Method VPT0224/VPT1817:

Dabrafenib and metabolites M7 and M8 were analysed at Aptuit using UHPLC-MS/MS. Calibration range was 1 to 1000 ng/mL. Adequate between- and within-run accuracy and precision was demonstrated. Stability in human plasma was shown for 3 freeze-thaw cycles, in room temperature for 24 hr, and at -20°C for 12 months for dabrafenib and 6 months for the metabolites. Cross-validation with Covance was made by analysing cross validation samples (3, 50 and 800 ng/mL) in a minimum of 6 replicates by both Aptuit and Covance, using the validated assay appropriate to each laboratory. For all of the cross validation test samples the % difference between laboratories was less than 20% and therefore within acceptance criteria for equivalence of the results of the two laboratories.

Method VPT0225/VPT1818:

The dabrafenib metabolite M4 was analysed at Aptuit using UHPLC-MS/MS. Calibration range was 5 to 5000 ng/mL. Adequate between- and within-run accuracy and precision was demonstrated. Stability in human plasma was shown for 5 freeze-thaw cycles, in room temperature for 24 hr, and at -20°C for 12 months. Cross-validation with Covance was made by analysing cross validation samples (15, 250 and 4000 ng/mL) in a minimum of 6 replicates by both Aptuit and Covance, using the validated assay appropriate to each laboratory. For all of the cross validation test samples the % difference between laboratories was less than 20% and therefore within acceptance criteria for equivalence of the results of the two laboratories.

Method GGGHPP:

Dabrafenib, M7, M8 and trametinib were analysed at Covance using HPLC with MS/MS detection. The validated concentration range was 1.00 to 1000 ng/ml for dabrafenib and metabolites, and 0.250 to 250 for trametinib. Long-term stability in frozen matrix K_2EDTA (-10 to -30°C and -60 to -80°C, respectively) was shown for 657 days for all analytes. Long-term stability in frozen matrix K_3EDTA was shown for 225 days. Freeze-thaw stability was shown for 5 cycles. The method was originally validated for K_2EDTA. QC samples prepared in human plasma K_3EDTA were evaluated to determine cross validation method performance from K_2EDTA to K_3EDTA. The results confirmed the acceptability of using K_3EDTA as anticoagulant. Cross validation against Aptuit was performed by comparing analysis results for QC samples. Acceptance criteria were met.

Method G83HPP:

Carboxy-dabrafenib was analysed at Covance using HPLC with MS/MS detection. The validated concentration range was 5.00 to 5000 ng/ml. Long-term stability in frozen matrix K_2EDTA was shown for 308 days in -10 to -30°C and for 682 days at -60 to -80°C. Long-term stability in frozen matrix K_3EDTA was shown for 99 days. Freeze-thaw stability was shown for 5 cycles. Cross validation of method performance from K_2EDTA to K_3EDTA confirmed the acceptability of using K_3EDTA as anticoagulant. Cross validation against Aptuit was performed by comparing analysis results for QC samples. Acceptance criteria were met.

Table 3. Method validation reports included in the current variation application

Document no.	method	Analyte	Vendor	Includes	Comment
2011N130965_01	VPT0224	dabrafenib, hydroxy-dabrafenib, desmethyl-dabrafenib	Aptuit	Addendum 1: Original full validation + additional long-term stability data	PARTLY NEW: Original method validation report submitted in the original MAA for Tafinlar. Addendum updated with long-term stability data, not previously submitted
2011N130964_01	VPT0225	carboxy-dabrafenib	Aptuit	Full validation	Original method validation report Addendum 1 was submitted for the original MAA for Tafinlar.
2013N184873_00	VPT1817	dabrafenib, hydroxy-dabrafenib, desmethyl-dabrafenib	Aptuit	Cross validation with Covance, cross validation of anticoagulants, effects of haemolysed and hyperlipidaemic plasma	PARTLY NEW: Method based on VPT0224, but more details added
2013N184872_00	VPT1818	carboxy-dabrafenib	Aptuit	Cross validation with Covance, cross validation of anticoagulants, effects of haemolysed and hyperlipidaemic plasma	PARTLY NEW: Method based on VPT0225, but more details added
2015N244953_00	GGGHPP	dabrafenib, hydroxy-dabrafenib, desmethyl-dabrafenib, trametinib	Covance	Addendum 2: Original full validation + Additional stability data, cross validation for counter ion, cross validation with Aptuit	PARTLY NEW: Original method validation report submitted in the original MAA for Mekinist. Addendum 2 not previously submitted
2015N266466_00	G83HPP	carboxy-dabrafenib	Covance	Addendum 1: Original full validation + Additional stability data, cross validation for counter ion, cross validation with Aptuit	NEW: Method not previously assessed.

Pharmacokinetic and pharmacodynamic analysis

Pharmacokinetic data were obtained from the phase II study BRF113928 in patients with Stage IV BRAF V600E mutant NSCLC.

In Cohort A, subjects took dabrafenib 150 mg twice daily under fasting conditions. In Cohort B, Cohort C and crossover from Cohort A, subjects took the combination of dabrafenib 150 mg twice daily and trametinib 2 mg once daily.

Only sparse PK sampling was performed. PK samples were collected at study visits in Week 3, Week 6, Week 12 and Week 18. At Week 3, one sample was obtained prior to study treatment administration (between 8 to14 hours after the evening dose dabrafenib on the previous day) and a second sample was obtained 1 to 3 hours following the morning dose. For the rest of the scheduled visits, only one PK sample was obtained 2 to 14 hours after the most recent dose of study treatment or prior to the second daily dose on that day, i.e. samples could be denoted either post-dose or pre-dose for dabrafenib. Date and exact time of PK sample and of most recent dose were recorded.

All PK concentration data analyses were conducted for the monotherapy cohort and combination cohorts, separately. No formal comparison was conducted between the Monotherapy Cohort A and the Combination Cohorts B and C. Standard summary statistics were calculated. In addition, the pharmacokinetics of dabrafenib and trametinib was determined using a non-linear mixed effects modelling approach. Post-hoc estimates of population PK parameters including apparent clearance (CL/F), Vc/F, and absorption rate constant (ka) were estimated, when data permitted.

Exposure-response analyses were conducted among subjects who have PK concentration data from the Week 3 visit. All analyses were conducted for the monotherapy cohort and combination cohorts, separately. All analyses were exploratory in nature and included analyses of tumour response/PFS based on Investigator or IRC assessments.

2.4.2.2. Results

Summary statistics of plasma concentration data

Summary statistics were presented for pre- and post-dose plasma concentrations at all study visits (Week 3, 6, 12 and 18). For results of the population pharmacokinetic analysis of these data, see below.

Pre- and post-dose concentrations at week 3 were obtained within a relatively narrow time window (8-14 after dabrafenib evening dose and 1-3 hr after morning dose) and summary statistics are presented below. The variability was high.

Table 4. Summary of pre- and post-dose plasma concentration data for dabrafenib, metabolites and trametinib at WEEK 3 visit, in Cohort A and Cohort B (Study BRF113928)

	Monotherapy (Cohort A)		Combination (Cohort B)	
Analyte	Pre-dose (8-14 hr after last dabrafenib dose)	Post-dose (1-3 hr after morning dose)	Pre-dose (8-14 hr after last dabrafenib dose)	Post-dose (1-3 hr after morning dose)
Dabrafenib				
Median (ng/ml) [N]	40.4 [20]	2038 [63]	70.2 [19]	1640 [37]
Min-Max	7 - 230	16 - 4433	15 - 3340	412 - 4140
Hydroxy-dabrafenib				
Median (ng/ml) [N]	68 [20]	919 [63]	74.5 [19]	860 [37]
Min-Max	18 - 335	5 - 2421	13 - 1230	192 - 2120
Carboxy-dabrafenib				
Media (ng/ml)n [N]	3854 [20]	4265 [63]	3830 [19]	4395 [38]
Min-Max	698 - 15930	26 - 24463	1960 - 10300	180 - 13500
Desmethyl-dabrafenib				
Median (ng/ml) [N]	283 [20]	330 [63]	313 [19]	445 [37]
Min-Max	112 - 1355	4 - 1044	70 - 809	4 - 1730
Trametinib				
Median (ng/ml) [N]	N/A	N/A	12.9 [26]	24.6 [37]
Min-Max			9 - 25	11 - 42

In the figure below, dabrafenib plasma concentration is plotted vs. time after dose for Cohort A and Cohort B. There are no apparent differences between the Cohorts. No comparison of trametinib concentrations with and without dabrafenib can be made as trametinib was only administered in combination.

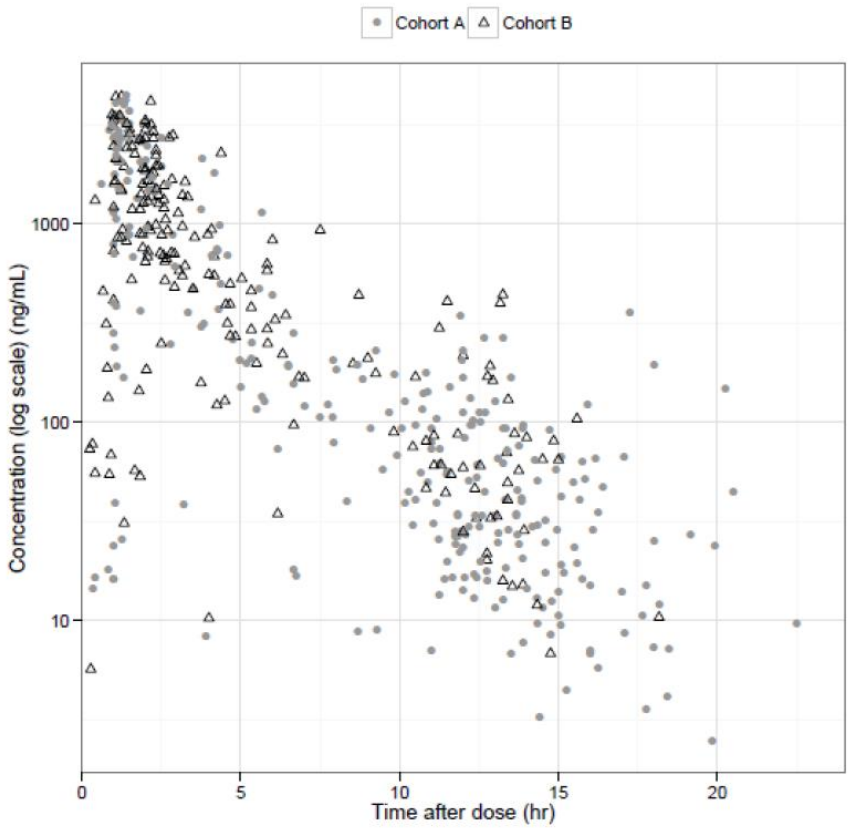


Figure 2. Comparison of concentration vs time data for dabrafenib at Weeks 3, 6, 12 and 18 in Cohort A (monotherapy) and Cohort B (combination with trametinib)

Population pharmacokinetic analysis

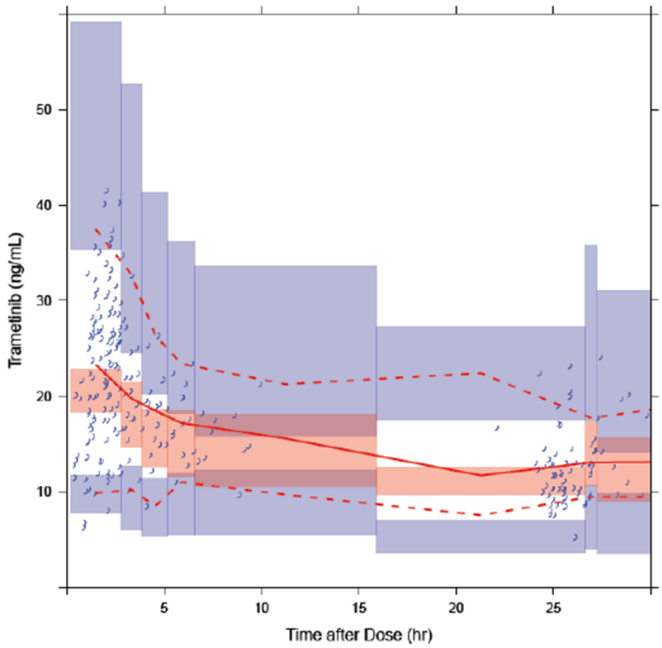
Data from Study BRF113928 were included in this popPK analysis. Subjects in Cohort A received dabrafenib monotherapy (150 mg BID) and subjects in Cohort B and C received dabrafenib (150 mg BID) in combination with trametinib (2 mg QD). PK samples were obtained at Week 3 (pre-dose and 1-3 hours post-dose) and pre-dose or 2-14 hours post-dose at Weeks 6, 12 and 18. A total of 146 subjects had measured plasma concentration data and were included in the population pharmacokinetic analyses with 76 subjects who received dabrafenib monotherapy and 70 subjects who received dabrafenib and trametinib combination. The number of dabrafenib concentrations included in the analyses was 536.

The previously established dabrafenib and trametinib population PK models were used to describe the PK data from this study and provide posthoc estimates of oral clearance (CL/F) and volume of distribution (VC/F).

An external validation approach was used to confirm the data from the current study were consistent with data used in prior analyses (primarily melanoma). The final model parameters used to describe the dabrafenib and trametinib monotherapy and combination data from study BRF113220 (GlaxoSmithKline Document Number 2012N144949_02) were fixed to the final parameter estimates (fixed and random effects).

Trametinib popPK

The previous developed trametinib model and parameter estimates to predict the exposure of the subjects in the BRF113928 study was deemed to not describe the trametinib data adequately. The data from BRF113928 was subsequently pooled with the previous model data and a study specific covariate was introduced on CL/F and Vc/Fm, see Figure 3 for visual predictive check of updated model. The updated model was fitted to the pooled data. Study effect was found to be statistically significant on CL/F (0.86 (95%CI: 0.80, 0.92)) and Vc/F (0.49 (95%CI: 0.33, 0.65)). The median post-dose (1 to 3 hr) trametinib concentrations levels at Week 3 in the current study were 1.21 times higher than previously reported for study BRF113220 for the same dosing regimen.

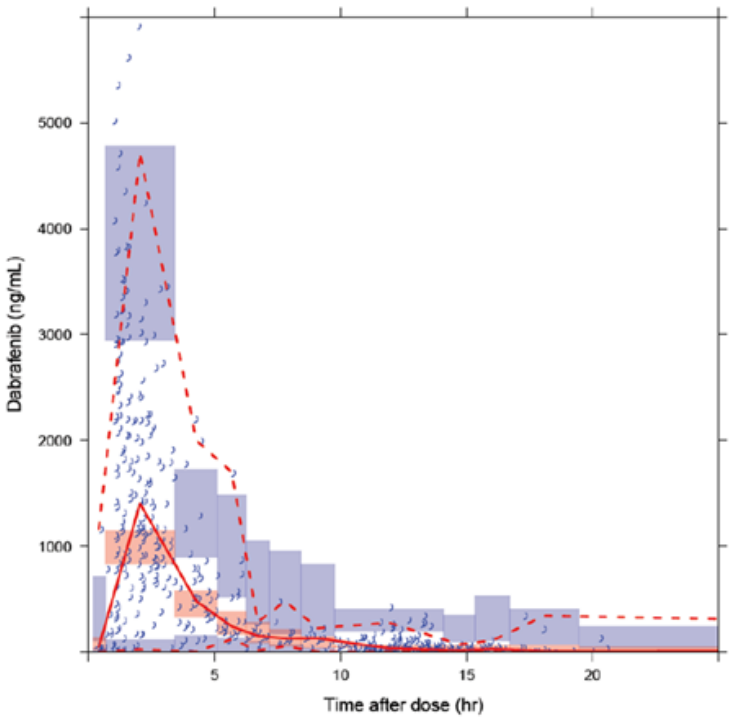


Red solid and dotted lines are median, 2.5th, and 97.5th percentiles for observed data. Red area is the 95% CI around the simulated median. Blue areas are the 95% CI around the simulated 2.5th and 97.5th percentiles. Blue symbols are the observations.

Figure 3. Trametinib visual predictive check (prediction corrected) of updated model

Dabrafenib popPK

Dabrafenib PK was deemed by the applicant to be adequately described by the previously developed two-compartment PK model structure including significant covariates of weight (CL/F, Vc/F, Q/F), sex (CL/F) and a small effect of the combination with trametinib (CL/F). Some parameters including Ka, tlag, power of dependence of CLIND,SS on absorbed dose (Alpha), T50, Q/F and oral peripheral volume of distribution (Vp/F) and the associated inter-subject variability, were fixed as the data collected in the study would be unlikely to allow accurate estimation due to lack of dose range and lack of samples collected during the absorption phase. Visual predictive check is shown in Figure 4 and parameter estimates in **Error! Reference source not found.**



Red solid and dotted lines are median, 2.5th, and 97.5th percentiles for observed data. Red area is the 95% confidence interval (CI) around the simulated median. Blue areas are the 95% CI around the simulated 2.5th and 97.5th percentiles. Blue symbols are the observations.

Figure 4. Dabrafenib visual predictive check (prediction correction)

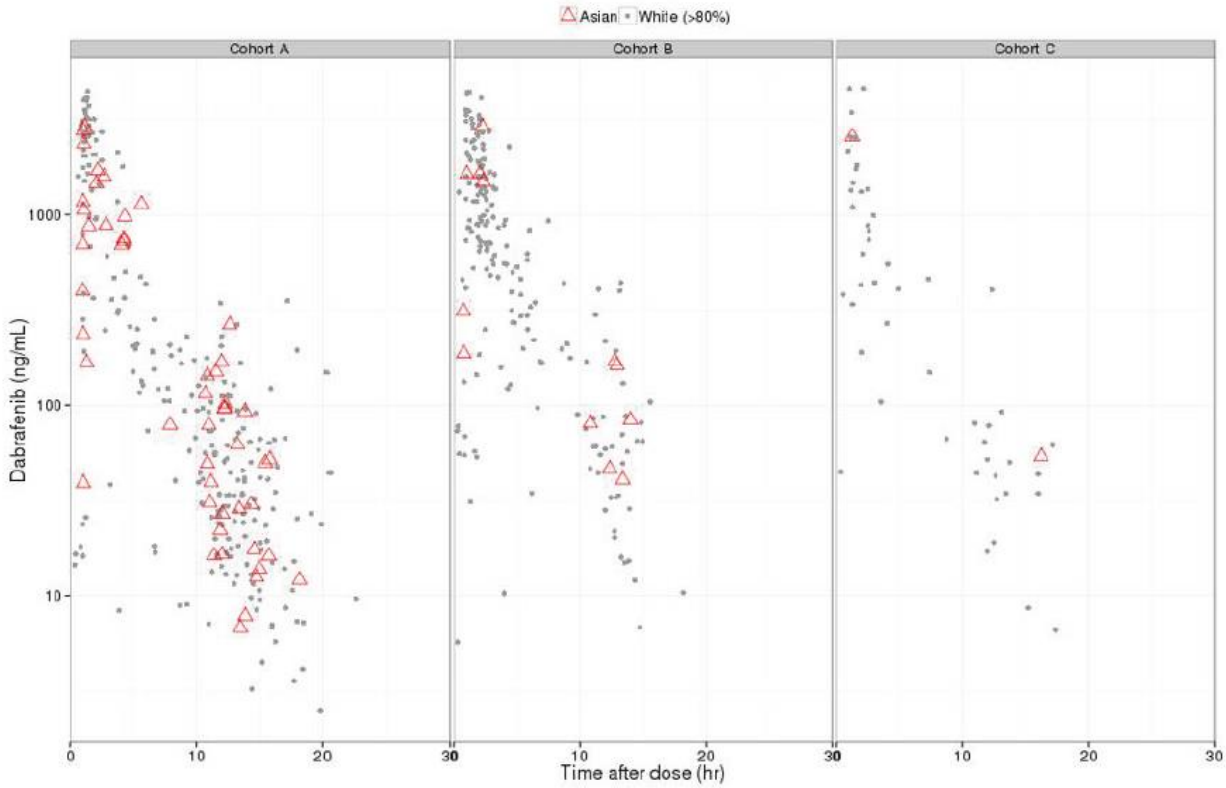
Table 5. Dabrafenib population parameter estimates of the previously developed model and model containing only BRF113928 study data

Parameter		Previous Model Estimate	95% CI	BRF113829 Data only Estimate	95% CI
Fixed Effect					
CL_0/F [L/hr]	θ_1	16.7	15.3, 18.1	16.0	12.2, 19.7
V_c/F [L]	θ_2	58.5	53.6, 63.4	52.1	42.5, 61.7
V_p/F [L]	θ_3	197	178, 216	197	FIX
Q/F [L/hr]	θ_4	4.63	4.15, 5.11	4.63	FIX
K_a [1/hr]	θ_5	1.22	1.06, 1.38	1.22	FIX
Tlag [hr]	θ_6	0.415	0.413, 0.417	0.415	FIX
$CL_{IND,SS}/F$ [L/hr]	θ_7	18.6	17.7, 19.5	18.6	FIX
Alpha	θ_8	1.02	0.947, 1.09	1.02	FIX
T_{50} [hr]	θ_9	60.7	41.5, 79.9	60.7	FIX
F_{GEL}	θ_{10}	0.586	0.536, 0.636	0.586	FIX
CL_{WT}	θ_{11}	0.300	0.185, 0.415	0.492	0.110, 0.874
CL_{SEX}	θ_{12}	0.899	0.865, 0.933	0.851	0.734, 0.967
V_{CWT}	θ_{13}	0.593	0.387, 0.799	0.00956	-0.532, 0.551
Q_{WT}	θ_{14}	1.06	0.622, 1.46	4.08	2.56, 5.59
CL_{COMBO}	θ_{15}	0.625	0.578, 0.672	0.655	0.506, 0.804
ω^2_{CL0}	$\Omega(1,1)$	0.362	0.306, 0.418	0.472	0.233, 0.711
Covar ω_{CL} ω_{Vc}	$\Omega(1,2)$	0.304	0.252, 0.356	0.341	0.159, 0.522
ω^2_{Vc}	$\Omega(2,2)$	0.298	0.234, 0.362	0.246	0.0852, 0.407
ω^2_{Q}	$\Omega(3,3)$	0.760	0.621, 0.899	1.17	0.579, 1.76
ω^2_{Ka}	$\Omega(4,4)$	1.18	0.994, 1.37	1.18	FIX
σ^2_{prop}	$\Sigma(1,1)$	0.298	0.284, 0.312	0.292	0.229, 0.355
σ^2_{add} [ng/mL]	$\Sigma(2,2)$	1(FIX)		1	FIX

hr = hour; CI, confidence interval; CL0/F, apparent initial clearance; Vc/F, apparent volume of central compartment; Vp/F, apparent volume of peripheral compartment; Q/F, apparent inter-compartmental clearance; Ka, absorption rate constant; tlag, absorption lag-time; CLIND,SS/F, apparent inducible clearance at steady state; Alpha, power of dependence of CLIND,SS on absorbed dose (LDOS*FGEL); LDOS, last administered dose; FHPMC, relative bioavailability of HPMC capsule to gelatin capsule ; T50, half-life of clearance induction; CLWT, Effect of weight on CL/F; CLSEX, Effect of sex on CL/F; VcWT, Effect of weight on Vc/F; QWT, Effect of weight on Q/F; CLCOMBO, Effect of combo on CLIND,ss/F; ω^2CL0, ω^2Vc, ω^2Vp, ω^2Q, ω^2Ka, variances of the respective inter-individual random effects; Covar=covariance; σ^2_{prop}, variance of the proportional component of the residual error model; σ^2_{add}, variance of the additive component of the residual error model.

Effect of Race

Race was tested as a covariate on CL/F of dabrafenib and found to be similar in Asians and Caucasians. In the dabrafenib dataset, only 19 (13%) subjects were of Asian race. However, the exposure in these subjects was within the range observed in other subjects (**Error! Reference source not found.**). The Applicant also provided a summary table of exposure data from other studies, indicating no clinically relevant differences in exposure between Japanese and Caucasian subjects (Figure 5).



Open triangles represent observed concentrations from Asian race; closed circles represent observed concentrations from all other races.

Figure 5. Individual dabrafenib concentration-time data from BRF113928 by race

Table 6. Dabrafenib AUC(0-τ) on Day 21 after 150 mg BID alone or in combination with trametinib 2 mg QD

Study/Treatment	AUC(0-τ)[1] ng*hr/mL
BRF113220/Monotherapy n=11 (Caucasian Subjects)	4663 (44) [3511, 6194]
BRF116056/Monotherapy n=5 (Japanese Subjects)	5900 (33) [3946, 8829]
BRF113220/Combination n=12 (Caucasian Subjects)	5886 (40) [4608, 7517]
MEK116885/Combination n=6 (Japanese Subjects)	10138 (33) [7230, 14216]

[1] Data is presented as geometric mean (CVb%) [95% CI]

Exposure response analysis

Exposure-response analysis was performed using the smaller dataset (n=17) for which pre-dose concentrations (no more than one hour before the dose and between 8 to 14 hours after the previous dose) in Week 3 were available. The response endpoints evaluated were investigator-assessed ORR and PFS.

2.4.3. Discussion on clinical pharmacology

Only sparse PK data were collected in study BRF113928. The presented summary statistics of these data are not considered very informative, given the diverse time points over the dosing intervals at which the samples were drawn.

Both the popPK model for trametinib and the popPK for dabrafenib show bias at high concentrations. Population PK results for trametinib show that CL/F and VC/F were estimated to be around 15 and 50 percent lower respectively, compared to the previously reported values for melanoma patients. This is however not considered clinically relevant.

The estimated model parameters show similar PK for dabrafenib as previously reported. Based on the population pharmacokinetic analysis, the MAH suggests the inclusion in section 5.2 of the Tafinlar SmPC that there are no significant differences in the pharmacokinetics of dabrafenib between Asian and Caucasian patients. Although this conclusion is based on only 19 Asian patients (13%) in the dabrafenib Pop-PK dataset, the suggested comparable exposure is supported by independent data obtained in Japanese patients. This, together with the lack of differences with respect to safety between Asian/Japanese and Caucasian patients, warrants the conclusion that no dose adjustment is needed in Asian patients (see sections 4.2 and 5.2 of the SmPC).

There were no substantial changes made to the information in the PK section of the SmPC. The proposed changes in the pharmacokinetic information of the SmPCs are of editorial nature and are acceptable.

2.4.4. Conclusions on clinical pharmacology

The proposed changes in the pharmacokinetic sections of the SmPC are mainly editorial and are considered acceptable.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

The proposed dosing regimen of dabrafenib 150 mg orally BID (i.e., twice daily) and trametinib 2 mg orally OD (i.e., once daily) in patients with metastatic NSCLC harbouring a BRAF V600 mutation is the same as what has already been approved for the indication in metastatic melanoma, and has been selected on the basis of nonclinical data and clinical efficacy and safety data essentially performed in melanoma patients (See EPAR for WS-0736).

The dabrafenib-trametinib combination regimen was assessed in the Phase I/II Study BRF113220 (a study investigating dabrafenib alone versus combined dabrafenib and trametinib (D+T) in patients with BRAF V600 mutation-positive metastatic melanoma).

Study BRF113220 was performed to determine the optimal dosage of trametinib when administered in combination with dabrafenib for the treatment of patients with BRAF V600 mutation positive stage IIIc or IV melanoma. In Part B of study BRF113220 patients were enrolled in escalating dose cohorts of dabrafenib and trametinib.

In Part C of this study the efficacy of two dose levels were evaluated in patients with BRAF V600 positive melanoma: dabrafenib 150 mg twice daily with trametinib 1 mg once daily (150/1 dose) and dabrafenib 150 mg twice daily with trametinib 2 mg once daily (150/2 dose). The 150/2 dose was selected over the 150/1 dose based on increased clinical activity. Data from the primary analysis of Study BRF113220 Part C showed a confirmed ORR of 76% and 50%, and median duration of response (DoR) of 10.5 months and 9.5 months for the combination 150/2 dose and the 150/1 dose, respectively (Flaherty et al 2012b).

2.5.2. Main study

Title of Study BRF113928: A Phase II study of the BRAF inhibitor dabrafenib as a single agent and in combination with the MEK inhibitor trametinib in subjects with BRAF V600E mutation positive metastatic (stage IV) non-small cell lung cancer (NSCLC)

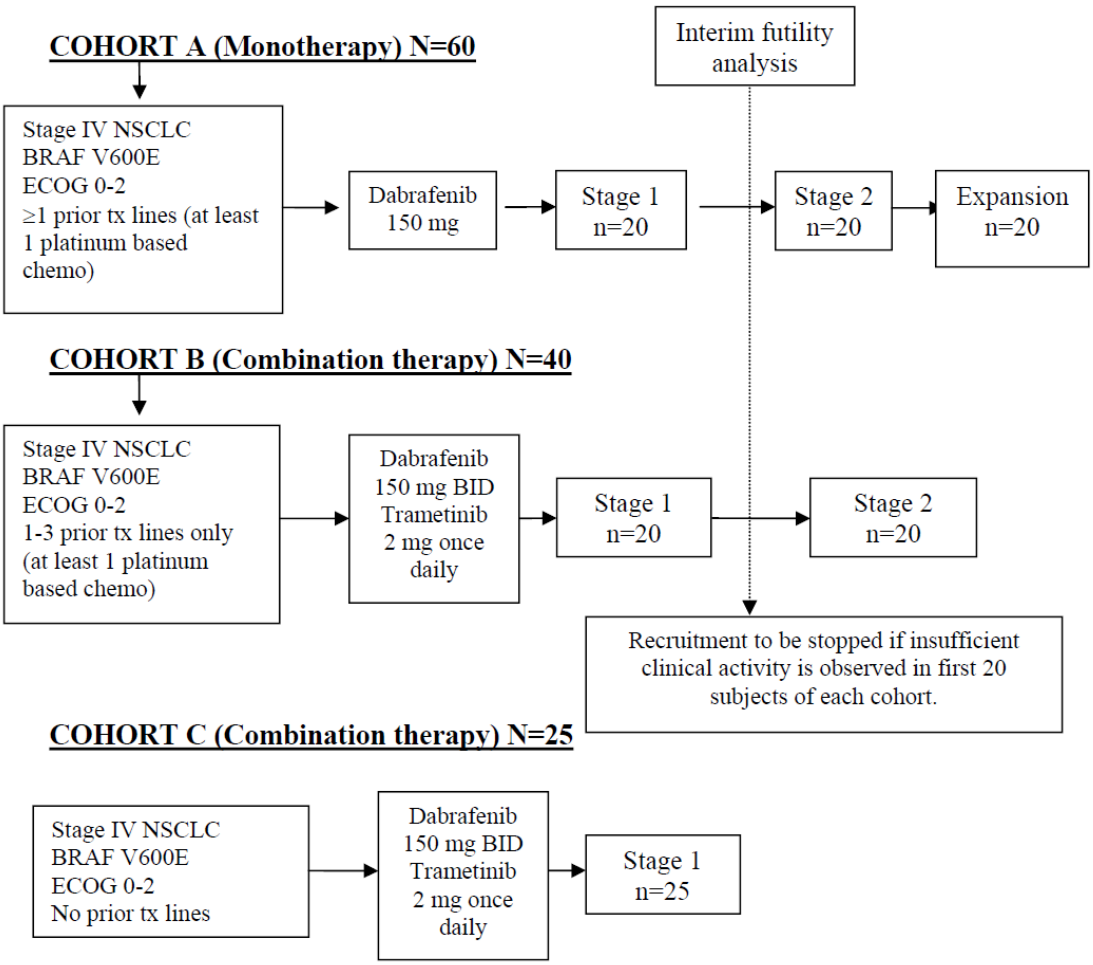


Figure 6. Design of the pivotal BRF113928 study

Methods

Study participants

Key Inclusion Criteria

- Histologically or cytologically-confirmed diagnosis of NSCLC Stage IV NSCLC determined to be BRAF V600E mutation-positive.
- For Cohorts A and Cohort B, documented tumour progression after receiving at least one prior approved platinum-based chemotherapy regimen for advanced stage/metastatic NSCLC
- Measurable disease according to RECISTv1.1
- ECOG 0-2.
- Subjects with concomitant EGFR/ALK mutations were eligible if previously treated with EGFR or ALK inhibitors

Key Exclusion Criteria

- Active brain metastases
- Increased cardiovascular risk (defined)
- History of retina vein occlusion and interstitial lung disease (trametinib)

BRAF V600E testing from local laboratory was used for enrolment eligibility. Central confirmation testing for the BRAF V600E mutation (according to the Oncomine Universal Dx Test performed on the Ion Torrent PGM Dx System- Life Technology Corporation, a Thermo Fisher Scientific company- selected as the companion diagnostic).

Treatments

Patients with metastatic NSCLC harbouring a BRAF V600E mutation were enrolled into the three cohorts sequentially:

Cohort A - dabrafenib 150 mg BID as monotherapy: patients were required to have relapsed or progressed after receiving at least one prior platinum-based chemotherapy regimen before enrolment.

Cohort B and C – dabrafenib 150 mg BID and trametinib 2 mg OD: In cohort B patients were required to have relapsed or progressed after receiving at least one platinum-based chemotherapy but not to have received more than three prior systemic anti-cancer therapies.

Patients were instructed to take dabrafenib at 150 mg twice daily, either as monotherapy or in combination with trametinib with approximately 200 mL of water under fasting conditions, either one hour before or 2 hours after a meal. Subjects were encouraged to take their doses at 12 hour intervals and at similar times every day. For combination therapy, subjects were instructed to take trametinib 2 mg once daily along with the first dose of dabrafenib 150 mg as described above, while the second dose of dabrafenib 150 mg was administered approximately 12 hours after the morning dose.

In all cohorts, patients were treated until clinical or radiological disease progression according to RECIST 1.1 criteria based on investigator assessment, unacceptable toxicity, and/or consent withdrawal. Tumour assessments were performed every 6 weeks until week 36, and every 12 weeks thereafter (±7 days). Upon discontinuation of study drug, information was collected on any subsequent anti-cancer therapy, survival and disease progression if not previously confirmed. Survival and new anti-cancer therapy follow-up were to be continued until a minimum of 70% of the subjects had died in each cohort or five years have passed since the last subject's first dose, whichever came first.

In Cohort A cross-over to dabrafenib-trametinib combination treatment after progression on dabrafenib monotherapy was allowed.

Objectives

The primary objective of the BRF113928 trial was to evaluate objective tumour response rate (ORR) based on investigator assessment (according to RECIST 1.1) in patients with Stage IV BRAF V600E mutant NSCLC administered dabrafenib as a single-agent (Cohort A) and in combination with trametinib (Cohorts B and C).

Secondary objectives included evaluation of duration of response (DoR), progression free survival (PFS), and overall survival (OS) in the three cohorts, evaluation of pharmacokinetics and safety.

Exploratory objectives were: a) to explore the molecular mechanisms of sensitivity and resistance to dabrafenib as single agent (cohort A) or in combination with trametinib (cohort B and C); b) to explore exposure-response relationship, tumour size measurements or other clinical or safety endpoints; c) to explore a circulating cell free DNA blood based test to determine whether BRAF mutation in cfDNA correlate with mutations in the tumour tissue; d) to explore cytokine and angiogenesis factors as potential soluble markers associated with tumour response; e) to evaluate ORR and DoR in patients crossing over from the dabrafenib monotherapy arm to the combination arm; f) pharmacogenetics.

No formal comparison was conducted between the monotherapy and combination cohorts.

Outcomes/endpoints

The primary study endpoint was ORR: percentage of patients who had a confirmed complete response (CR) or partial response (PR) according to RECIST 1.1 criteria based on investigator assessment. Patients with not evaluable (NE) or missing best overall response were treated as non-responders. The best overall response was the best confirmed response recorded from the start of treatment until disease progression, start of new anti-cancer therapy, or death, whichever occurred earlier. Best confirmed response based on Independent Review Committee (IRC) assessment was also provided as supportive analysis, together with a concordance analysis between investigator and IRC assessment.

Secondary endpoints included:

- Duration of response (DoR): time (in months) from first documented evidence of CR or PR until documented disease progression or death due to any cause, whichever was first, in the subgroup of patients with a confirmed CR and PR.

- PFS: interval (in months) between the first dose of study medication and the earlier date of disease progression or death due to any cause.

- OS: time (in months) from first dose of study drug until the date of death due to any cause.

If a subject had not progressed, was alive, and did not start new anti-cancer therapy, PFS was censored at the date of the last adequate assessment. Patients who had not died were censored at the date of last contact (as recorded in the eCRF). Subjects who permanently discontinue study treatment for reasons other than disease progression, but do not withdraw from the study, will continue to have efficacy assessments (radiological) until documentation of progression or until the beginning of new anti-cancer therapy. Radiological assessment was every 6 weeks until week 6, and then every 12 weeks.

All subjects underwent local screening to define their BRAF V600E mutation status as part of the entry criteria. Subsequently, the BRAF mutation status for subjects enrolled on study was confirmed in a central laboratory. An exploratory biomarker analysis was also to be performed.

Exploratory analyses were performed in order to evaluate disease burden at baseline, time to response, maximum tumour size reduction, time to progression for the immediate prior anti-cancer therapy for metastatic disease, and lesion volumetric data.

Sample size

The sample size for each cohort was planned so that statistical power of at least 90% and alpha levels of less than 0.05 were achieved for Investigator assessed ORR.

-Monotherapy Cohort A: The sample size was based on the hypothesized ORR for dabrafenib using a two-stage Green-Dahlberg design, in order to enable early stopping for futility and obtaining more precision for the estimate of ORR. The monotherapy cohort was further expanded (amendment) to enrol 60 subjects to provide a better precision of the ORR estimate for dabrafenib monotherapy.

-Combination Cohort B: The sample size was based on the hypothesized ORR for dabrafenib and trametinib combination using a two-stage Green-Dahlberg design. The planned sample size was 40 subjects with 20 subjects in each stage. This design corresponded to a type I error of 0.032 and power of 92.2% to conclude that ORR was >30% from the data assuming that the ORR in the population was ≥55% (H0: ORR ≤30%, H1: ORR ≥55%).

-Combination Cohort C: The sample size for Cohort C was based on the hypothesized ORR for dabrafenib and trametinib combination in subjects who had not received prior systemic anti-cancer therapies for metastatic disease using a 1-stage exact-binomial design. The planned sample size was 25 subjects. This design corresponds to a type I error of 0.044 and a power of 92.2% to conclude that ORR was >30% from the data assuming that the ORR in the population was ≥ 60% (H0: ORR ≤30%, H1: ORR ≥60%).

Randomisation

This was a single arm study, therefore patients were not randomised.

Blinding (masking)

This was an unblinded study.

Statistical methods

The analysis populations were defined separately for Monotherapy Cohort A and the Combination Cohorts B and C.

- Monotherapy Cohort A:

1- Monotherapy All Treated Population: all subjects who received at least one dose of study treatment, irrespective of their prior lines of treatment for metastatic disease.

2- Monotherapy Second-Line Plus Population: all subjects who had relapsed or progressed after receiving at least one line of prior anti-cancer therapy for metastatic disease.

3- Monotherapy First-Line Population: all subjects who had not received any prior anti-cancer therapy for metastatic disease.

4- Crossover Population: subjects who were assigned to monotherapy cohort and elected to crossover to combination treatment following disease progression on monotherapy.

- Combination Cohorts B and C:

1- Combination All Treated Population: all subjects who received at least one dose of study treatment, irrespective of their prior lines of treatment for metastatic disease.

2- Combination Second-Line Plus Population: all subjects who had relapsed or progressed after receiving at least one line of prior anti-cancer therapy for metastatic disease.

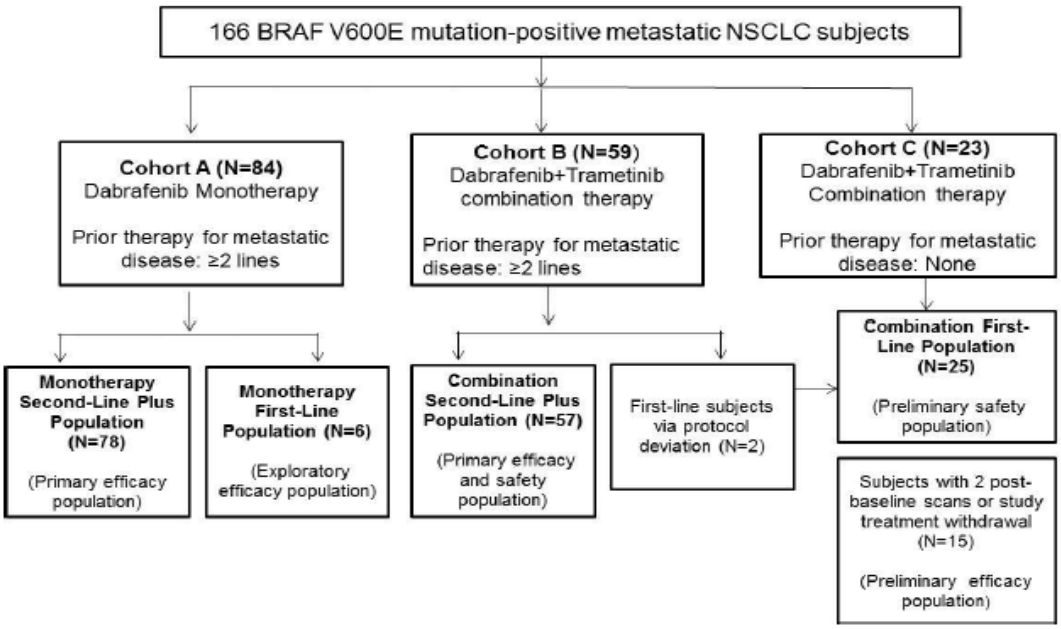
3- Combination First-Line Population: all subjects who had not received any prior anti-cancer therapy for metastatic disease. It was the primary population for efficacy analysis for subjects enrolled in Combination Cohort C, but could also include any subjects who were receiving combination treatment as first-line in Cohort B via a protocol deviation.

No formal comparisons between cohorts were planned. Each cohort had one primary endpoint (ORR) and the Green-Dahlberg design (cohort A, B) had one interim analysis on ORR for futility conducted by the independent data monitoring committee.

ORR, DoR, PFS had primary analysis by investigator and sensitivity analysis by independent reviewer; this was on both the primary population (2^{nd} line plus/ 1^{st} line all treated) and the secondary population (2^{nd} line/ 1^{st} line BRAF V600E centrally confirmed). For the cross-over population, one analysis i.e. by investigator was conducted. ORR: subjects with unknown or missing best response were considered non-responders. Exact confidence intervals were calculated. Time to event endpoints (PFS, OS, DoR) were analysed using Kaplan-Meier methodology.

Results

Participant flow



Recruitment

The first patient was enrolled on 5 August 2011. A total of 46 centers across 11 countries enrolled 166 patients. Patients were enrolled sequentially into the three different cohorts based on the number of prior lines of systemic treatment for metastatic disease. At the time of the data cutoff of the submitted CSR (07-Oct-2015), Cohort A and Cohort B had completed enrollment while Cohort C was actively enrolling.

- In Cohort A, 84 subjects were enrolled between 05-Aug-2011 and 28-Feb-2014 and received dabrafenib as a single-agent, 78 of which as second or later line (Monotherapy Second Line Plus Population) and 6 as first line (Monotherapy First-Line Population).

As per inclusion criteria, all subjects in the Monotherapy All Treated Population (N=84), except one, tested BRAF V600E positive by local laboratories prior to start of the treatment. This subject had wild type BRAF and was enrolled, however, a protocol deviation was not recorded at the time of analysis (data cut-off 30-Apr-2014).- In Cohort B, 59 subjects were enrolled between 16-Dec-2013 and 14-Jan-2015 and received dabrafenib in combination with trametinib, of which 57 patients as second, third or fourth line of therapy (Combination Second Line Plus Population) and 2 patients enrolled as first line due to protocol deviation (included in the Cohort C for results analysis).

Fifty five (55) subjects tested positive for BRAFV600E by local laboratory prior to the start of combination treatment. One subject had a V600 mutation (by a local lab which cannot differentiate V600K or V600E), and another subject had a T TF1 and CK5/6 mutation together with BRAF V600E mutation.

- In Cohort C, 23 subjects were enrolled since 07-Apr-2015 up to 07-Oct-2015 (data cut-off date) and received dabrafenib in combination with trametinib as first line (Combination First line Population).

The 23 subjects were tested positive for BRAFV600E by local laboratory prior to start of the combination treatment. Two subjects (8%) tested positive for more than one mutation in BRAF: one subject had BRAFV600E and V600K, while another subject had BRAFV600E as well as BRAF G469A and BRAF D594G mutations. After database close, both cases were queried. For the 1st subject, the method used at local laboratory couldn't differentiate V600E vs V600K. This was recorded as a protocol deviation. The 2nd subject was confirmed to have only BRAFV600E mutation.

A total of 16 subjects crossed over from dabrafenib monotherapy (Cohort A) to dabrafenib and trametinib combination treatment within 4 weeks of radiologic disease progression and are referred to as the "Crossover Population".

Conduct of the study

The original study protocol was amended 9 times. Relevant amendments consisted of amendment 7 (allowed expansion cohort A with additional 20 patients, and allowed inclusion in cohort A of treatment naïve patients for metastatic disease), amendment 8 (added the dabrafenib/trametinib combination therapy cohort [n=40], restricted to a maximum of 3 the numbers of prior systemic therapies allowed in cohort B, and allowed cross-over from monotherapy to combination arm after progression), amendment 9 (added cohort C with 25 evaluable first line patients and expanded cohort B from 40 to approximately 60 patients).

Baseline data

Table 7. Baseline patient characteristics - BRF113928 study (data cut-off 7-Oct-2015)

		Combination		Monotherapy
		2nd Line Plus (N=57)	1st Line (N=25)	2nd Line Plus (N=78)
Age (years)	n	57	25	78
	Mean	65.1	70.8	64.0
	SD	10.14	9.50	10.29
	Median	64.0	68.0	66.0
	Min.	41	55	28
	Max.	88	91	85
Age group (years)	n	57	25	78
	≥18 - <65	29 (51%)	6 (24%)	36 (46%)
	≥65 - <75	17 (30%)	12 (48%)	33 (42%)
	≥75 - <85	9 (16%)	4 (16%)	8 (10%)
	≥85	2 (4%)	3 (12%)	1 (1%)
Age group (years)	n	57	25	78
	<65	29 (51%)	6 (24%)	36 (46%)
	≥65	28 (49%)	19 (76%)	42 (54%)
Age group (years)	n	57	25	78
	<75	46 (81%)	18 (72%)	69 (88%)
	≥75	11 (19%)	7 (28%)	9 (12%)
Sex	n	57	25	78
	Female	28 (49%)	15 (60%)	39 (50%)
	Male	29 (51%)	10 (40%)	39 (50%)
Ethnicity	n	57	25	78
	Hispanic Or Latino	1 (2%)	1 (4%)	1 (1%)
	Not Hispanic Or Latino	56 (98%)	24 (96%)	77 (99%)
Race	n	57	25	78
	White	49 (86%)	23 (92%)	59 (76%)
	Asian	4 (7%)	1 (4%)	17 (22%)
	Black or African American	2 (4%)	0	2 (3%)
	Native Hawaiian or Other Pacific Islander	0	1 (4%)	0

In the combination 2nd-line Plus population, 6 patients were current smokers (11%) and 35 patients (61%) were former smokers, while 16 patients (28%) had never smoked. For the 41 current and former smokers, the median number of smoking pack years was 30 pack years (range: 2 to 94 smoking pack years).

In the combination 1st-line population, most of the patients (15 patients; 60%) were former smokers; 8 patients (32%) had never smoked. For the 17 current or former smokers, the median number of smoking pack years was 10 (range: 0 to 49 pack years).

In the monotherapy 2nd-line Plus population, most of the patients (46 patients; 59%) were former smokers, 29 patients (37%) had never smoked. For the 49 current or former smokers, the median number of smoking pack years was 30.0 (range: 0 to 94 pack years).

Table 8. Baseline disease characteristics - BRF113928 study (data cut-off 7-Oct-2015)

	Combination		Monotherapy
	2nd Line Plus (N=57)	1st Line (N=25)	2nd Line Plus (N=78)
Primary Tumor Type			
Non-Small Cell Lung	57 (100%)	25 (100%)	78 (100%)
Time Since Diagnosis (months)			
n	55	21	76
Min.	2.6	1.0	2.1
Median	14.80	2.00	14.80
Max.	64.9	63.2	88.9
Histology			
Adenocarcinoma	53 (93%)	22 (88%)	75 (96%)
Adenosquamous Carcinoma - Predominantly Adenocarcinoma	1 (2%)	0	0
Adenosquamous Carcinoma - Predominantly Squamous Cell Carcinoma	0	1 (4%)	1 (1%)
Bronchioloalveolar	2 (4%)	0	0
Bronchioalveolar Carcinoma, Mucinous Type	0	0	1 (1%)
Large Cell Carcinoma, Adenocarcinoma	0	0	1 (1%)
Large Cell Lung Cancer	1 (2%)	1 (4%)	0
Non Small Cell Carcinoma Without Other Precision	0	1 (4%)	0
Histological Grade			
Grade Cannot Be Assessed	32 (56%)	15 (60%)	26 (33%)
Well Differentiated	7 (12%)	3 (12%)	6 (8%)
Moderately Differentiated	4 (7%)	3 (12%)	14 (18%)
Poorly Differentiated	14 (25%)	4 (16%)	22 (28%)
Undifferentiated	0	0	4 (5%)
Unknown	0	0	6 (8%)
Time Since Last Progression (months)			
n	54	8	71
Median (Min-Max)	1.2 (0.1-14.7)	1.7 (0.4-7.4)	1.1 (0.2-6.8)
Number of Prior Radiotherapy Regimens			
0	41 (72%)	20 (80%)	49 (63%)
1	13 (23%)	5 (20%)	21 (27%)
>1	3 (5%)	0	8 (10%)

The ECOG Performance Status (PS) at baseline for all enrolled patients was 1 in 61% of the patients, 2 in 11% of the patients and 0 in 28% of the patients.

Almost all subjects enrolled in combination therapy (with the exception of one in the first-line population who was Stage III and enrolled due to a protocol deviation) had Stage IV cancer at screening.

Table 9. Prior therapies - BRF113928 study

	Combination	Monotherapy
	2nd Line Plus (N=57)	2nd Line Plus (N=78)
Number of Chemotherapy Regimens		
0	0	0
1	40 (70%)	39 (50%)
2	12 (21%)	16 (21%)
3	4 (7%)	11 (14%)
4	1 (2%)	5 (6%)
>4	0	7 (9%)
Number of Platinum-based Chemotherapy for metastatic disease		
0	1 (2%)	3 (4%)
1	50 (88%)	66 (85%)
2	5 (9%)	7 (9%)
3	1 (2%)	2 (3%)
Number of Radiotherapy Regimens		
0	41 (72%)	49 (63%)
1	13 (23%)	21 (27%)
2	3 (5%)	7 (9%)
3	0	1 (1%)
Number of Small Molecule Targeted Therapy Regimens		
0	49 (86%)	54 (69%)
1	8 (14%)	23 (29%)
3	0	1 (1%)
Number of Biologic Therapy Regimens		
0	54 (95%)	66 (85%)
1	3 (5%)	11 (14%)
3	0	1 (1%)

Data cut-offs: 07-Oct-2015 (Combination), 30-Apr-2014 (Monotherapy)

Numbers analysed

The number of patients included in the efficacy analysis populations is reported in the table below.

Table 10. Efficacy analysis populations – BRF113928 Study

Analysis Population	Number of Patients
Combination Second-Line Plus	57
Combination First-Line	25 (baseline characteristics) 15 (preliminary efficacy)[a]
Monotherapy Second-Line Plus	78

a: Preliminary efficacy analysis: at the cut-off date 01 Oct 2015, 15 patients had at least 2 post-baseline disease assessments or had discontinued study medication for any reason prior to their second post-baseline disease assessment.

Outcomes and estimation

Cohort A: Monotherapy Second-Line Plus Population:

Primary endpoint: ORR

Table 11. Summary of best response based on investigator and IRC (RECIST 1.1) for Second Line plus all treated patients in the monotherapy cohort – BRF113928 Study.

	Total (N=78)	
	Investigator-Assessed	IRC-Assessed
Best Response		
n	78	78
Complete Response	0	0
Partial Response	25 (32%)	18 (23%)
Stable Disease	19 (24%)	15 (19%)
Non-CR/Non-PD	0	9 (12%)
Progressive Disease	23 (29%)	25 (32%)
Not Evaluable	11 (14%)	11 (14%)
Response Rate		
CR+PR	25 (32.1%)	18 (23.1%)
95% Confidence Interval	(21.9%, 43.6%)	(14.3%, 34.0%)
Disease control rate		
CR+PR+SD	44 (56.4%)	42 (53.8%)
95% Confidence Interval	(44.7%, 67.6%)	(42.2%, 65.2%)

Data cut-off: 30-Apr-2014

Per Investigator assessment, the updated ORR after 6 months of follow-up from primary analysis (21-Nov-2014 data cut-off) was consistent with the primary analysis: the updated ORR was 33.3% (95% CI: 23.1%, 44.9%).

Per IRC assessment, for those with measurable disease at baseline, the updated ORR showed a slightly improved response to treatment with an ORR of 32.8% (95% CI: 21.6%, 45.7%, 1 pt with CR (2%)).

Table 12. Overall Response Rate by Demographic Characteristics (Monotherapy Second-Line Plus Population)

Sub-group category	Overall Response Rate (Investigator Assessment)			Overall Response Rate (IRC Assessment)		
	N	CR+PR	95% CI	N	CR+PR	95% CI
Gender, n (%)						
Male	39	31	(17.0, 47.6)	33	24	(11.1, 42.3)
Female	39	33	(19.1, 50.2)	31	32	(16.7, 51.4)
Age (Years), n(%)						
< 65	36	31	(16.3, 48.1)	30	33	(17.3, 52.8)
≥ 65	42	33	(19.6, 49.5)	34	24	(10.7, 41.2)
By Race, n (%)						
Asian	17	29	(10.3, 56.0)	15	20	(4.3, 48.1)
Non-Asian	61	33	(21.3, 46.0)	49	31	(18.3, 45.4)
Smoking History, n (%)						
Non-Smoker	29	48	(29.4, 67.5)	23	48	(26.8, 69.4)
Smoker	49	22	(11.8, 36.6)	41	17	(7.2, 32.1)
ECOG PS, n (%)						
0	16	19	(4.0, 45.6)	13	23	(5.0, 53.8)
1	50	40	(26.4, 54.8)	43	33	(19.1, 48.5)
2	12	17	(2.1, 48.4)	8	13	(0.3, 52.7)
Prior Anti-Cancer Therapies, n (%)						
1	40	38	(22.7, 54.2)	31	39	(21.8, 57.8)
≥ 2	38	26	(13.4, 43.1)	33	18	(7.0, 35.5)

Note: Only includes results from subjects with measurable disease at baseline; data cut-off: 30-Apr-2014

Secondary endpoint: DoR

Table 13. Duration of Response (Monotherapy Second-Line Plus Population)

	Monotherapy Second-Line Plus N=78	
	Investigator Assessment	IRC Assessment
Number of Subjects with Confirmed Response[1], n (%)		
N	25	18
Progressed or died (event)	12 (48)	6 (33)
Censored, follow-up ended	0	3 (17)
Censored, follow-up ongoing	13 (52)	9 (50)
Estimates for Duration of Response (Months)[2]		
Median	11.8	NE
95% CI	(5.4, NE)	(4.2, .NE)

NE=Not estimable
[1] Number of subjects with confirmed complete or partial response [RECIST 1.1].
[2] Confidence Intervals estimated using the Brookmeyer Crowley method.

At the time of the updated analysis (21-Nov-2014), the median DoR was mature with 77% of the responders progressing. The estimated median DoR was 9.6 months and 9.9 months based on Investigator and IRC assessments, respectively.

Secondary endpoint: PFS

Table 14. Summary of Progression-Free Survival (Monotherapy Second-Line Plus Population)

	Monotherapy Second-Line Plus N=78	
	Investigator Assessment	IRC Assessment
Number of Subjects, n (%)		
Progressed or died (event)	48 (62)	47 (60)
Censored, follow-up ended	8 (10)	10 (13)
Censored, follow-up ongoing	22 (28)	21 (27)
Estimates for Progression Free Survival (Months)[1]		
Median	5.5	5.5
95% CI	(2.8, 7.3)	(2.8, 6.8)

[1] Confidence Intervals estimated using the Brookmeyer Crowley method

At the time of the updated analysis (21-Nov-2014), the PFS data was mature with 76% of the subjects having PFS events; estimated median PFS: was 5.5 months, 95% CI: 3.4, 7.3 for Investigator and 5.5 months, 95% CI: 2.8, 6.9 for IRC)

Other secondary endpoints:

Overall Survival: At the time of the latest updated analysis (data cut-off date of 07-Oct-2015), with an additional 18 months of follow-up from the primary analysis, majority of subjects (55 subjects; 71%) had died. The estimated median OS remained at 12.7 months (95% CI: 7.3, 16.3).

Time to response: Majority of the subjects (18 of 25 responders per investigator assessment) showed response at Week 6 (first post-baseline assessment). None of the subjects had an initial response after Week 36 from the start of treatment.

Maximum target lesion reduction (30-Apr-2014): Based on Investigator assessment, 33 subjects (45.8%) had tumour reductions of ≥ 30% from baseline in the target lesions. As per IRC, a similar proportion of subjects (28 subjects, 47.5%) had tumour reductions of ≥ 30% from baseline in target lesions.

Cohort B: Combination therapy:

Primary endpoint: ORR

Table 15. Summary of Best Confirmed Response Based on Investigator Assessment (Combination First-Line and Second-Line Populations, 7-Oct-2015)

	Combination First-Line N=15 [1]	Combination Second-Line Plus N=57
Best confirmed response, n (%)		
Complete Response	1 (7)	2 (4)
Partial Response	7 (47)	34 (60)
Stable Disease	4 (27)	9 (16)
Progressive Disease	2 (13)	7 (12)
Not Evaluable	1 (7)	5 (9)
Response Rate, n (%)		
CR+PR	8 (53.3)	36 (63.2)
95% Confidence Interval	(26.6, 78.7)	(49.3, 75.6)
Disease Control Rate, n (%)		
CR+PR+SD	12 (80.0)	45 (78.9)
95% Confidence Interval	(51.9, 95.7)	(66.1, 88.6)

[1] Note: of the 25 subjects enrolled at the time of the preliminary analysis (data cut-off date of 07-Oct-2015) only 15 subjects had two post-baseline tumor assessments or had discontinued from the study and were included in the ORR analysis

Table 16. Summary of Best Confirmed Response Based on IRC Assessment (Combination First-Line and Second-Line Treated Populations, 7-Oct-2015)

	Combination First-Line N=15 [1]	Combination Second-Line Plus N=57
Best Confirmed Response, n (%)		
Complete Response	1 (7)	0
Partial Response	6 (40)	36 (63)
Stable Disease	4 (27)	4 (7)
Non-CR/Non-PD	-	3 (5)
Progressive Disease	3 (20)	8 (14)
Not Evaluable	1 (7)	6 (11)
Response Rate, n (%)		
CR+PR	7 (46.7)	36 (63.2)
95% Confidence Interval	(21.3, 73.4)	(49.3, 75.6)
Disease Control Rate, n (%)		
CR+PR+SD+Non-CR/Non-PD	11 (73.3)	43 (75.4)
95% Confidence Interval	(44.9, 92.2)	(62.2, 85.9)

[1] Note: of the 25 subjects enrolled at the time of the preliminary analysis (data cut-off date of 07-Oct-2015) only 15 subjects had two post-baseline tumor assessments or had discontinued from the study and were included in the ORR analysis.

Table 17. Summary of Best Confirmed Response by Demographic Characteristics (Combination Second-Line Plus Population)

Sub-group category	N	Response rate (Investigator) CR+PR n (%)	95% CI	Response rate (IRC) CR+PR n (%)	95% CI
Gender					
Male	29	58.6	(38.9, 76.5)	65.5	(45.7, 82.1)
Female	28	67.9	(47.6, 84.1)	60.7	(40.6, 78.5)
Age (Years)					
< 65	29	79.3	(60.3, 92.0)	72.4	(52.8, 87.3)
≥ 65	28	46.4	(27.5, 66.1)	53.6	(33.9, 72.5)
By Race					
White	49	67.3	(52.5, 80.1)	65.3	(50.4, 78.3)
Asian	4	25.0	(0.6, 80.6)	50.0	(6.8, 93.2)
African American	2	50.0	(1.3, 98.7)	50.0	(1.3, 98.7)
Other	2	50.0	(1.3, 98.7)	50.0	(1.3, 98.7)
Smoking History					
Non-Smoker	16	62.5	(35.4, 84.8)	56.3	(29.9, 80.2)
Former Smoker	35	68.6	(50.7, 83.1)	68.6	(50.7, 83.1)
Current smoker	6	33.3	(4.3, 77.7)	50.0	(11.8, 88.2)
Baseline ECOG PS					
0	17	58.8	(32.9, 81.6)	58.8	(32.9, 81.6)
≥ 1	40	65.0	(48.3, 79.4)	65.0	(48.3, 79.4)
Prior Anti-cancer therapies					
1	38	68.4	(51.3, 82.5)	68.4	(51.3, 82.5)
≥ 2	19	52.6	(28.9, 75.6)	52.6	(28.9, 75.6)

Secondary endpoint: DoR

Table 18. Summary of Duration of Response (Combination Second-Line Plus Population)

	Combination Second-Line Plus N=57	
	Investigator Assessment	IRC Assessment
Number of Subjects with Confirmed Response[1], n (%)		
N	36	36
Progressed or died (event)	18 (50)	18 (50)
Censored, follow-up ended	0	3 (8%) [3]
Censored, follow-up ongoing	18 (50)	15 (42)
Estimates for Duration of Response (Months)[2]		
Median	9.0	9.0
95% CI	(6.9, 18.3)	(5.8, 17.6)

[1] Number of subjects with confirmed complete or partial response [RECIST 1.1]
[2] Confidence Intervals estimated using the Brookmeyer Crowley method
[3] 3 subjects had no radiological PD evaluated by IRC before discontinuing from the study

Secondary endpoint: PFS

Table 19. Summary of Progression- Free Survival (Combination Second-Line Plus Population)

	Combination Second-Line N=57	
	Investigator Assessment	IRC Assessment
Subject Status, n (%)		
Progressed or died (event)	32 (56)	34 (60)
Censored, follow-up ended	3 (5)	4 (7)
Censored, follow-up ongoing	22 (39)	19 (33)
Estimates for Progression Free Survival (Months)[1]		
Median	9.7	8.6
95% CI	(6.9, 19.6)	(5.2, 19.1)

[1] Confidence Intervals estimated using the Brookmeyer Crowley method

Table 20. Summary of Progression-Free Survival by Demographic Characteristics (Second-Line Plus Population)

Sub-group category		Investigator Assessment		IRC Assessment	
	N	Estimates for PFS (Months)	95% CI	Estimates for PFS (Months)	95% CI
Gender					
Male	29	11.1	(5.2, 19.6)	10.2	(3.3, 19.1)
Female	28	9.6	(5.4, NE)	7.0	(4.4, NE)
Age (Years)					
< 65	29	11.1	(5.5, 19.6)	16.8	(5.5, 19.1)
≥ 65	28	9.6	(4.4, NE)	6.3	(3.1, 9.8)
By Race					
White	49	9.8	(7.4, 19.6)	9.7	(5.5, 19.1)
Asian	4	5.4	(2.5, 5.4)	3.3	(1.4, NE)
African American	2	13.6	NE	-	-
Other	2	3.8	(0.8, 6.9)	3.8	(0.8, 6.9)
Smoking History					
Non-Smoker	16	7.7	(4.4, NE)	5.7	(3.1, NE)
Former Smoker	35	10.2	(6.9, 19.6)	9.7	(5.2, 19.1)
Current smoker	6	2.2	(0.8, NE)	-	(0.8, NE)
Baseline ECOG PS					
0	17	19.6	(4.4, 19.6)	10.2	(1.4, 16.8)
≥ 1	40	9.6	(5.4, 13.6)	7.2	(4.4, 19.1)
Prior Anti-cancer therapies					
1	38	9.8	(5.6, NE)	9.7	(5.2, NE)
≥ 2	19	8.6	(2.2, 19.6)	8.2	(2.9, 19.1)

NE: Not Evaluable

Other secondary endpoints:

Overall Survival: At the time of the primary analysis (data cut-off date of 07-Oct-2015), 23 subjects (40%) had died, and the estimated median OS was 17.6 months (95% CI: 14.3, NE).

Time to Response: At the time of the primary analysis (data cut-off date of 07-Oct-2015), the majority of subjects by Investigator and IRC assessments (27/36, 75% and 30/36, 83% respectively) responded by Week 6 (first post-baseline assessment).

Maximum Target Lesion Reduction

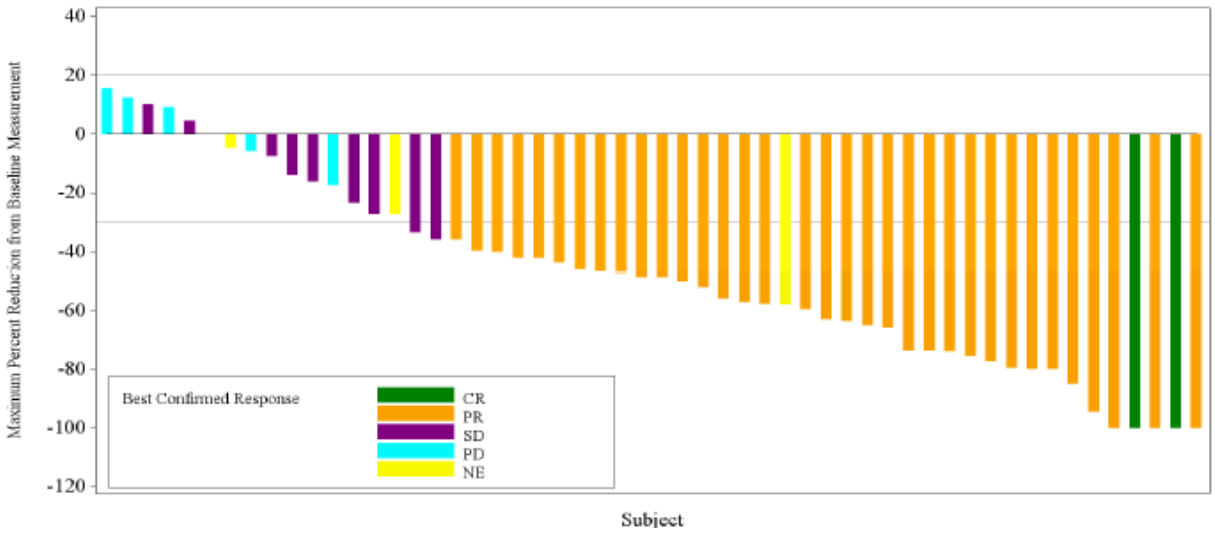


Figure 7. Plot of Investigator-assessed percent change at maximum reduction from baseline sum of diameters by best confirmed response (Combination Second-Line Plus Population) – data cut-off 7-Oct-2015

Updated results (data cut-off 8-Aug-2016)

Cohort C of study BRF113928 finished enrolling 34 patients on 28-Dec-2015. Combined with the 2 patients who did not receive prior systemic anti-cancer therapy in Cohort B due to protocol deviation, the efficacy data from these 36 patients who were treated with the combination of dabrafenib and trametinib as first-line treatment were analysed and key results are provided with the responses to Request for Supplementary Information.

At the cut-off date (8-Aug-2016), all patients had completed at least 6 months follow-up from the first post-baseline tumour assessment or had discontinued from the study. The median follow-up time was approximately 10.4 months.

In Cohort B, at the data cut of 8-Aug-2016, the mature duration of response (DoR) of Combination 2nd Line Plus population was 9.8 months (95% CI: 6.9-16.0 months) with 71% of patients (27/38) who had progressed or died, and median PFS (mPFS) was 10.2 months (95% CI: 6.9-16.7 months) by investigator assessment with 72% of patients (41/57) who had progressed or died.

The median overall survival (OS) was 18.2 months (95% CI: 14.3-NE months) with an event rate of 58%.

Table 21. Summary of efficacy based on investigator and independent radiology review

Endpoint	**Analysis**	**Combination 1st Line N=36[1]**	**Combination 2nd Line Plus N=57[1]**	**Monotherapy 2nd line Plus N=78**
Overall confirmed response n (%) (95% CI)	By Investigator By IRC	22 (61.1) (43.5, 76.9) 22 (61.1) (43.5, 76.9)	38 (66.7) (52.9, 78.6) 36 (63.2) (49.3, 75.6)	25 (32.2) (21.9, 43.6) 18 (23.1) (14.3, 34.0)
Median DoR Months (95% CI)	By Investigator By IRC	NE[2] (8.3, NE) NE (6.9, NE)	9.8 (6.9, 16.0) 12.6 (5.8, NE)	9.6 (5.4; 15.2) 9.9 (4.2; NE)
Median PFS Months (95% CI)	By Investigator By IRC	-[3] -[3]	10.2 (6.9, 16.7) 8.6 (5.2, 16.8)	5.5 (3.4; 7.3) 5.5 (2.8; 6.9)
Median OS Months (95% CI)	-	24.6 (11.7, NE)[4]	18.2 (14.3, NE)	12.7 (7.3, 16.3)

[1] Data cut-off: 8th August 2016
[2] NE: Not Evaluable
[3] Median PFS currently not estimable
[4] Event rate for OS calculation was 28% and hence the defined median value still needs to mature

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22. Summary of Efficacy for trial BRF113928

Title: A Phase II study of the BRAF inhibitor dabrafenib as a single agent and in combination with the MEK inhibitor trametinib in subjects with BRAF V600E mutation positive metastatic (stage IV) non-small cell lung cancer.			
Study identifier	BRF113928		
Design	Phase II, multicenter, non-randomized, open-label, sequentially enrolling, non-comparative study investigating the effects of dabrafenib administered as a single agent and in combination with trametinib in adult patients with histologically- or cytologically-confirmed diagnosis of NSCLC stage IV and BRAF V600E mutation-positive.		
	First Subject enrolled in Cohort A: 05-Aug-2011 • Last Subject enrolled in Cohort A: 28-Feb-2014 • First Subject enrolled in Cohort B: 16-Dec-2013 • Last Subject enrolled in Cohort B: 14-Jan-2015 • First Subject enrolled in Cohort C: 07-Apr-2015 • Last Subject enrolled in Cohort C: 28-Dec-2015. This cohort was actively enrolling at the time of initial data cut-off (07-Oct-2015) for the study report submitted in original NSCLC application. • Last Subject completion: Study is ongoing.		
Hypothesis	Non-comparative study		
Treatments groups	Cohort A: Dabrafenib monotherapy second line and further		Monotherapy (Dabrafenib 150 mg twice daily), in BRAF V600E positive NSCLC patients relapsed or progressed after receiving at least one platinum-based chemotherapy prior to enrolment. N= 84
	Cohort B: Dabrafenib-trametinib combination therapy Second Line Plus		Combination Therapy (Dabrafenib 150 mg twice daily and Trametinib 2 mg once daily), in BRAF V600E positive NSCLC patients relapsed or progressed after receiving at least one platinum-based chemotherapy prior to enrollment but not to have received more than three prior systemic anti-cancer therapies. N=57
	Cohort C: Dabrafenib-Trametinib First Line		Combination Therapy (Dabrafenib 150 mg twice daily and Trametinib 2 mg once daily), in BRAF V600E positive NSCLC patients not pre-treated with any prior systemic anti-cancer therapies for metastatic disease. N=25
Endpoints and definitions 06	Primary endpoint	ORR	Confirmed ORR based on Investigator assessed response according to RECIST 1.1, which was defined as the percentage of subjects who had a confirmed complete response (CR) or partial response (PR).
	Secondary endpoint	DoR	Duration of response: Defined for the subset of subjects with confirmed CR or PR, as the time from first documented evidence of CR or PR until the time of first documented disease progression or death due to any cause.
	Secondary endpoint	PFS OS	Progression-free survival: Defined as the interval between first dose and the earliest date of disease progression or death due to any cause. Overall survival: was defined as the time (in months) from first dose until death due to any cause.
Data cut-off	07 Oct 2015		

Results and Analysis

Analysis description	**Analysis based on IRC**			
Analysis population and time point description	Intent to treat (all patients treated with at least one treatment dose)			
Descriptive statistics and estimate variability	Treatment group	Cohort A	Cohort B	Cohort C
	Number of subject	N= 78	N=57	N=25
	ORR 95%CI	23.1% (CR: 0) (14.3-34.0)	63.2% (CR: 4%) (49.3-75.6)	46.7% (CR: 7%) (21.3-73.4)
	DoR (median, mo) 95%CI	9.9 (4.2-NE)	9.6 (5.4-15.2)	

	PFS (median, mo) 95%CI OS (median, mo)	5.5 (2.8-6.9) 12.7 (NA)	8.6 (5.2-19.1) 17.6 (14.3, NE)	NA NA
Updated results (IRC) Data cut-off: 08 Aug 2016				
Descriptive statistics and estimate variability	Treatment group	Cohort A	Cohort B	Cohort C
	Number of subject	N= 78	N=57	N=36
	ORR 95%CI	23.1% (14.3-34.0)	63.2% (49.3-75.6)	61.1% (43.5-76.9)
	DoR (median, mo) 95%CI	9.9 (4.2-NE)	12.6 (5.8-NE)	NE
	PFS (median, mo) 95%CI OS (median, mo)	5.5 (2.8-6.9) 12.7 (NA)	8.6 (5.2-16.8) 18.2 (14.3, NE)	- 24.6 (11.7, NE)

Supportive study

Intergroupe Francophone de Cancérologie Thoracique (IFCT) study

The IFCT study provided contemporaneous real-life outcomes data for patients with NSCLC with and without a BRAF V600E mutation following treatment with available standard-of care therapies.

The purpose of this study, which was conducted in France, was to assess the characteristics, molecular profiles, and clinical outcomes of patients who were screened during a 1–year period from April 2012 to April 2013.

Of the 250 patients (1.4%) with BRAF mutations, 189 (1.07%) were determined to have a V600E BRAF mutation. Median age of the 189 patients with the BRAF V600E mutation was 66.4 years (range 42.9-88.7), 57.4% were men, 69.2% were smokers or former smokers, and 88.4% had adenocarcinoma.

Regarding patients with the BRAF V600E mutation, 65.7% received first-line treatment, with platinum-based chemotherapy being most common (49.0%), and 42.9% received second-line treatment, with platinum-based chemotherapy again being most common (16.1%).

ORR for patients with BRAF V600E-positive NSCLC receiving second-line standard-of-care therapies was 20.8% (95% CI: 9.8, 31.7), excluding those who received BRAF inhibitor treatment.

Also, ORRs for patients receiving first-line standard-of-care therapies were 30.3% (95% CI: 21.6, 38.9) and 29.6% (95% CI: 28.6, 30.6) for patients with BRAF V600E-positive NSCLC (excluding those who received BRAF inhibitor treatment) and for patients with NSCLC without any mutation, respectively (IFCT 2015).

Median overall survival (defined as the date of the molecular analysis assessment to the date of death or final follow-up) for patients with the BRAF V600E mutation was 17.2 months (95% CI: 11.5, not estimable [NE]) compared to 11.8 months (95% CI: 11.1, 12.5) for patients with no mutation. Median survival for patients with a BRAF V600E mutation excluding patients receiving BRAF inhibitor treatment was 15.2 months (95% CI: 9.6, NE).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

BRAF V600 mutation-positive NSCLC is a rare condition, representing 1-3% of non-squamous histology of the lung. Due to the well documented efficacy of dabrafenib and trametinib in BRAF V600 mutation-positive melanoma, foreseen high activity in BRAF V600 mutated NSCLC, the expected low activity of chemotherapy and the small target population, the MAH decided to conduct a single arm trial that included three cohorts of BRAF V600 mutated metastatic NSCLC which were enrolled sequentially: first cohort dabrafenib monotherapy in previously treated patients, followed by combination therapy in previously treated patients and finally combination therapy in treatment naïve patients.

It is not expected that safety would differ to a meaningful degree between melanoma and NSCLC and a randomisation between monotherapy and the combination therapy would have not been possible. The reasons for the implemented study design are understood in view of the rarity of the disease.

Efficacy data and additional analyses

Dabrafenib monotherapy: The confirmed ORR in 78 patients was 32% (investigator) and 23% (IRC) (protocol defined primary analysis). After an additional 6 months of follow-up for patients with measurable disease at baseline per IRC assessment, the IRC ORR was 33%. Based on treatment history, the within response rate to first-line platinum therapy was about 30% (12/39). Median PFS (investigator and IRC) was about 5.5 months, similar to reported treatment history TTP.

Dabrafenib + trametinib: In the second line plus setting the confirmed ORR was 63% (95% 49; 76%) by both investigator and IRC in 57 individuals. Median duration of response was found to be 9 months (investigator and IRC) and PFS 9.7 and 8.6 months (investigator and IRC) at an event rate of about 60%. About 80% of responses were observed at first imaging, i.e. at 6 weeks.

Thirty-six subjects were evaluable for response in the first-line setting and the reported ORR was 22/36, i.e. about 61%.

Results are considered as sufficiently convincing to conclude that combination therapy is efficacious.

At a response rate of 60% and PFS of 9 months, relevant anti-tumour activity has been shown. Based on experience from NSCLC studies in general, this is highly likely to translate into symptom reduction and delay in symptomatic progression.

Given the limited follow-up in the 1st line setting, the MAH is recommended to provide final mature efficacy results of Cohort C when available.

The OS results of the IFCT study appear to support the hypothesis that NSCLC patients with BRAF mutations present a different natural history compared to patients with no mutations, as median OS was longer in BRAF mutated NSCLC (15.2 -17.2 months independently on whether a BRAF targeted treatment was given) compared with patients without mutations (11.8 months), independent of the treatment received. Moreover, the data available do not seem to indicate a clear OS improvement with the combination trametinib-dabrafenib in the BRF113928 study (median OS 17.6 months) compared with the "historical" IFCT database (median OS 15.2-17.2 months). However, it is possible to exclude a detriment in OS. .

Exploratory biomarker analyses are currently being planned for the BRF113928 study and the MAH is recommended to submit the results of these "biomarker" analyses once available.

2.5.4. Conclusions on the clinical efficacy

The clinical efficacy of the combination of dabrafenib + trametinib in patients with V600 driven NSCLC irrespective line of therapy has been established. However the efficacy of Dabrafenib monotherapy in the treatment of patients with V600 driven NSCLC has not been established.

2.6. Clinical safety

Introduction

The safety profile for dabrafenib 150 mg twice daily in combination with trametinib 2 mg once daily in subjects with BRAF V600 mutation-positive NSCLC is derived from the Phase II study BRF113928 and consists of: a) dabrafenib and trametinib combination therapy arm in second line patients, n=57 (Cohort B); b) dabrafenib and trametinib combination therapy arm in first line patients, n=25 (Cohort C); c) dabrafenib monotherapy arm, n=84 (Cohort A). The safety results are also discussed in comparison with the safety observed for the approved indication in melanoma (n=559), which was based on 2 large randomized Phase III studies.

Patient exposure

The median daily dabrafenib dose was 295.8 mg in the pooled group of combination-treated patients, 290.6 mg in Cohort B (combination second line), 300 mg in Cohort C (combination first line) and 294.8 mg in Cohort A (monotherapy) of the pivotal BRF113928 study. The median daily trametinib dose was 2.0 mg in all of the combination cohorts.

Table 23. Duration of exposure to study drug in the combination populations

	Combination pooled	Combination second-line plus	Combination first-line
	N=82	N=57	N=25
	n (%)	n (%)	n (%)
Time on dabrafenib treatment (months) [1]			
Mean (SD)	7.61 (5.86)	9.36 (5.81)	3.62 (3.68)
Median (Min-Max)	5.75 (0.2-20.7)	10.55 (0.3-20.7)	3.32 (0.2-19.3)
Exposure category (months)			
< 3	24 (29)	12 (21)	12 (48)
3 to 6	19 (23)	8 (14)	11 (44)
> 6 to 9	7 (9)	6 (11)	1 (4)
> 9 to 12	14 (17)	14 (25)	0
> 12 to 24	18 (22)	17 (30)	1 (4)
Time on trametinib treatment (months)			
Mean (SD)	7.56 (5.92)	9.29 (5.91)	3.63 (3.68)
Median (Min-Max)	5.60 (0.2-21.1)	10.55 (0.3-21.1)	3.38 (0.2-19.2)
Exposure category (months)			
< 3	25 (30)	13 (23)	12 (48)
3 to 6	19 (23)	8 (14)	11 (44)
> 6 to 9	6 (7)	5 (9)	1 (4)
> 9 to 12	13 (16)	13 (23)	0
> 12 to 24	19 (23)	18 (32)	1 (4)

[1] The time on study drug does not exclude dose interruptions.

Table 24. Summary of exposure to dabrafenib and trametinib in the combination populations

Exposure	Combination pooled N=82		Combination second-line plus N=57		Combination first-line N=25	
	Dabrafenib 150 mg bid	Trametinib 2 mg once daily	Dabrafenib 150 mg bid	Trametinib 2 mg once daily	Dabrafenib 150 mg bid	Trametinib 2 mg once daily
Subject daily dose (mg) [1]						
n	82	82	57	57	25	25
Mean	261.2	1.8	252.8	1.8	280.4	1.9
SD	53.18	0.29	57.42	0.33	36.07	0.13
Median	295.8	2.0	290.6	2.0	300.0	2.0
Min.	126	1	126	1	170	2
Max.	300	2	300	2	300	2
Cumulative actual dose (mg)						
n	82	82	57	57	25	25
Mean	59920.1	414.5	72483.3	502.1	31276.0	214.9
SD	48947.63	330.34	49462.96	332.58	33879.76	224.68
Median	45237.5	310.0	71300.0	520.0	25500.0	180.5
Min.	1800	12	2400	16	1800	12
Max.	186300	1252	186300	1252	175800	1170

[1] The subject daily dose (the cumulative dose divided by the duration of exposure) is calculated for each subject first and the summary statistics are calculated based on the subject daily dose.

Adverse events

In the pivotal BRF113928 study, AEs were graded according to the CTCAE, Version 4.0. AEs were coded to the preferred term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA) dictionary.

Table 25. Overview of Adverse Events (AEs)

	Pooled Combination Therapy N=82 n (%)	Combination Therapy Second Line N=57 n (%)	Combination Therapy First Line N=25 n (%)	Monotherapy N=84 n (%)
Any AE	79 (96)	56 (98)	23 (92)	83 (99)
AEs related to study treatment	71 (87)	51 (89)	20 (80)	77 (92)
AEs leading to permanent discontinuation of study treatment	10 (12)	8 (14)	2 (8)	6 (7)
AEs leading to dose reduction	24 (29)	20 (35)	4 (16)	16 (19)
AEs leading to dose interruption	47 (57)	35 (61)	12 (48)	40 (48)
Any SAE	38 (46)	32 (56)	6 (24)	36 (43)
SAEs related to study treatment	23 (28)	19 (33)	4 (16)	24 (29)
Fatal SAEs	4 (5)	4 (7)	0	1 (1)
Fatal SAEs related to study treatment	0	0	0	1 (1)
Deaths	24 (29)	23 (40)	1 (4)	57 (68)[1]

[1] Seventeen (20%) of the deaths occurred within 30 days of last dose of study treatment, whereas 40 patients (48%) died more than 30 days after last dose of study treatment.

Table 26. Summary of all AEs occurring in greater than 10% of patients by preferred term in pooled combination and second and first line groups (data cut-off: 7-Oct-2015)

Preferred term	Pooled Combination Therapy N=82 n (%)[1]	Combination Therapy Second Line N=57 n (%)	Combination Therapy First line N=25 n (%)	Monotherapy Second Line N=84 n (%)
Any event	**79 (96)**	**56 (98)**	**23 (92)**	**83 (99)**
Pyrexia	37 (45)	26 (46)	11 (44)	31 (37)
Nausea	34 (41)	23 (40)	11 (44)	24 (29)
Vomiting	25 (30)	20 (35)	5 (20)	18 (21)
Diarrhoea	23 (28)	19 (33)	4 (16)	16 (19)
Decreased appetite	21 (26)	17 (30)	4 (16)	24 (29)
Asthenia	19 (23)	18 (32)	1 (4)	26 (31)
Dry skin	19 (23)	15 (26)	4 (16)	21 (25)
Oedema peripheral	19 (23)	13 (23)	6 (24)	3 (4)
Chills	15 (18)	13 (23)	2 (8)	13 (15)
Cough	15 (18)	12 (21)	3 (12)	24 (29)
Fatigue	15 (18)	10 (18)	5 (20)	25 (30)
Rash	15 (18)	12 (21)	3 (12)	16 (19)
Constipation	13 (16)	10 (18)	3 (12)	10 (12)
Arthralgia	12 (15)	11 (19)	1 (4)	16 (19)
Dyspnoea	12 (15)	10 (18)	2 (8)	17 (20)
Neutropenia	12 (15)	11 (19)	1 (4)	2 (2)
Anaemia	11 (13)	10 (18)	1 (4)	10 (12)
Headache	10 (12)	6 (11)	4 (16)	16 (19)
Pruritus	10 (12)	9 (16)	1 (4)	12 (14)
Blood alkaline phosphatase increased	9 (11)	9 (16)	0	5 (6)
Dizziness	9 (11)	8 (14)	1 (4)	7 (8)
Myalgia	9 (11)	6 (11)	3 (12)	12 (14)
Weight decreased	9 (11)	8 (14)	1 (4)	15 (18)
Hypotension	8 (10)	7 (12)	1 (4)	6 (7)

[1] 10% cutoff value for AEs presented in table is based on the Pooled combination column.

Table 27. Summary of all grade 3 or 4 AEs occurring in greater than or equal to 2% of patients by preferred term in pooled combination and combination treatment groups (data cut-off: 7-Oct-2015)

	Pooled Combination Therapy[1] N=82		Combination Therapy Second Line N=57		Combination Therapy First Line N=25
Preferred term	**n (%)[1]**	**n (%)[1]**	**n (%)**	**n (%)**	**n (%)**
	Grade 3	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3[2]**
Any Grade 3 / 4 event	**31 (38)**	**4 (5)**	**24 (42)**	**4 (7)**	**7 (28)**
Neutropenia	6 (7)	0	5 (9)	0	1 (4)
Hyponatraemia	4 (5)	1 (1)	3 (5)	1 (2)	1 (4)
Anaemia	2 (2)	1 (1)	2 (4)	1 (2)	0
Asthenia	2 (2)	0	2 (4)	0	0
Dehydration	2 (2)	0	2 (4)	0	0
Dyspnoea	2 (2)	0	2 (4)	0	0
Hypercalcaemia	2 (2)	0	2 (4)	0	0
Hypertension	2 (2)	0	2 (4)	0	0
Leukopenia	2 (2)	0	2 (4)	0	0
Pulmonary embolism	2 (2)	0	1 (2)	0	1 (4)
Rash	2 (2)	2 (2)	1 (2)	0	1 (4)
Squamous cell carcinoma of skin	2 (2)	0	2 (4)	0	0
Weight increased	2 (2)	0	1 (2)	0	1 (4)

[1] 2% cutoff value for grade 3 and 4 AEs presented in table is based on the Pooled combination column.
[2] There were no Grade 4 AEs in the first line combination treatment group.

Adverse events of special interest

For most of the AESI the time of onset was typically within the first three months of treatment.

Table 28. Adverse events of special interest in the combination population

	Combination pooled N=82		Combination second-line plus N=57		Combination first-line N=25	
	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)
Any event [1]	**22 (27)**	**74 (90)**	**18 (32)**	**52 (91)**	**4 (16)**	**22 (88)**
Pyrexia	1 (1)	39 (48)	1 (2)	28 (49)	0	11 (44)
Skin-related toxicities	2 (2)	24 (29)	1 (2)	18 (32)	1 (4)	6 (24)
Diarrhea	1 (1)	23 (28)	1 (2)	19 (33)	0	4 (16)
Edema	0	23 (28)	0	16 (28)	0	7 (28)
Bleeding events	3 (4)	18 (22)	2 (4)	15 (26)	1 (4)	3 (12)
Neutropenia	8 (10)	14 (17)	7 (12)	13 (23)	1 (4)	1 (4)
Hepatic disorders	3 (4)	12 (15)	3 (5)	11 (19)	0	1 (4)
Occular events	1 (1)	11 (13)	1 (2)	8 (14)	0	3 (12)
Hypersensitivity	0	9 (11)	0	9 (16)	0	0
Renal failure	3 (4)	7 (9)	3 (5)	7 (12)	0	0
Cardiac-related events	0	4 (5)	0	3 (5)	0	1 (4)
Deep vein thrombosis /pulmonary embolism	2 (2)	4 (5)	1 (2)	2 (4)	1 (4)	2 (8)
Hyperglycemia	0	3 (4)	0	3 (5)	0	0
Hypertension	2 (2)	3 (4)	2 (4)	3 (5)	0	0
Pancreatitis	1 (1)	3 (4)	1 (2)	3 (5)	0	0
cuSCC including keratoacanthoma	2 (2)	2 (2)	2 (4)	2 (4)	0	0
Non-cutaneous treatment-emergent malignancies	1 (1)	1 (1)	1 (2)	1 (2)	0	0
Pneumonitis	0	1 (1)	0	1 (2)	0	0

AESI categories are sorted in descending order of All grades frequency.
[1] No cases of uveitis or new primary melanomas were reported.

Pyrexia

In the BRF113928 study, overall pyrexia was the most common AESI reported with the combination treatment. Most of the events were mild to moderate in severity. Only one subject withdrew from the study due to pyrexia, and these events were effectively managed in a clinical setting with dose interruptions and anti-pyretics.

In the pooled combination group of the BRF113928 study (Cohort B and C), pyrexia was reported in 39 patients (48%), in 38 patients being of grade 1 or 2. Ten patients had pyrexia SAEs, but only one led to study withdrawal. Thirty-two patients had pyrexia events that were considered related to study treatment. Pyrexia was managed without dose reduction in the majority of patients (79%, 31/39), with 49% (19/39) of patients requiring drug interruption. The median time to onset of pyrexia events from the start of combination treatment was 21 days (range: 3 to 416 days), with 31% (12/39) of the subjects experiencing the event within 14 days of starting treatment. No relationship was observed between exposure and pyrexia.

The incidence and severity of pyrexia were increased slightly when dabrafenib was used in combination with trametinib (48%, 3% Grade 3) as compared to dabrafenib monotherapy (39%, 2% Grade 3).

Bleeding events

In the pooled combination treatment group (Cohort B and C), bleeding events were reported in 18 patients (22%), with haemoptysis, epistaxis, hematoma, haematuria, and purpura being reported in more than one patient. Three patients had grade 3 events (haemoptysis, haematuria, and gastric haemorrhage), while two of the bleeding events were fatal (retroperitoneal haemorrhage and subarachnoid haemorrhage). Both of the patients with the fatal bleeding events had confounding factors such as iatrogenic coagulopathy and cerebral aneurysm, and the investigator assessed them as not related to study drugs. In 7 patients (39%) bleeding events were characterized as serious, and in 4 patients the events were related to the combination treatment. Bleeding events were managed without dose modifications in 15 patients, while one subject required drug interruption.

The median time to onset of the first occurrence of haemorrhagic events for the combination of trametinib and dabrafenib was 94 days in the melanoma Phase III studies and 63.5 days in the NSCLC study for the patients who had received prior anti-cancer therapy.

Treatment-emergent malignancies

In Cohort B (combination second line plus), one patient had a non-cutaneous treatment-emergent malignancy (hepatocellular carcinoma) that was most likely present before the patient started study medications. Cutaneous squamous cell carcinoma (CuSCC)-related events were reported in 2 patients. In Cohort C (combination first line) there were no AESIs of treatment-emergent malignancies or CuSCC-related events. In Cohort A (monotherapy group), all treatment-emergent malignancies were cutaneous. CuSCC events were experienced by 15 patients (18%) and all were considered to be study treatment-related. The median time to onset of CuSCC events was 78 days, and 80% (12 of 15) of the patients experienced the event more than 28 days after starting study treatment. None of the subjects withdrew from the study due to these events. All the CuSCC events were managed without requiring any dabrafenib dose modification. The most commonly used treatment was surgical resection. Basal cell carcinoma (BCC) was reported in six patients and in five patients these BCC events were considered related to study drug.

In the integrated safety population of patients with metastatic melanoma and advanced NSCLC, cuSCC occurred in 4% (24/641) of patients receiving dabrafenib in combination with trametinib.

Skin-related events (excluding CuSCC, Kerato-Acantoma)

In the combination treatment group (Cohort B and C), skin-related events (excluding CuSCC and KA) were reported in 24 subjects (29%), with rash (15 subjects, 18%) and erythema (5 subjects, 6%) being the most commonly reported. The event was considered treatment-related in 71% (17/24) of cases. All subjects with the exception of two had grade 1-2 events (2 pts had grade 3 rash). None of the events were characterized as serious, and none of the subjects withdrew from the study due to skin-related events. Only one subject required drug interruption and no other subjects required dose modifications. The median time to onset of skin-related events was 37 days (range: 1 to 253 days). At the time of the data-cut off for this analysis, the skin-related events had resolved in majority of the subjects (79%, 19/24). The median duration of the events was 50 days (range: 2 to 347 days), with 95% (21/22) of the subjects having a resolution after 10 days.

Diarrhoea

In the combination treatment group (Cohort B and C), diarrhoea events were reported in 23 patients (28%), all being grade 1-2 events with the exception of one grade 3 event. The event was considered to be related to treatment in 74% (17/23) of cases. One subject had a serious event, and none of the subjects withdrew from the study due to diarrhoea. 87% (20/23) of these subjects did not require dose modifications to manage these events, while three subjects each required a dose reduction and drug interruption. The median time to onset of diarrhoea from the start of combination treatment was 21 days (range: 1 to 314 days). At the time of the data-cut off for this analysis, diarrhoea events had resolved in majority of the subjects (78%). The median duration of the events was three days (range: 1 to 42 days), with 60% (12/20) of these subjects having a resolution within 5 days.

Oedema events

In the combination treatment group (Cohort B and C), oedema events were reported in 23 subjects (28%), with peripheral oedema being the most commonly reported (19 pts, 23%). All subjects had grade 1-2 events. The event was considered to be related to treatment in 65% (15/23) of cases. None of the events was considered as serious, required dose modification neither was the cause of treatment discontinuation. The median time to onset of oedema events was 42days (range: 20 to 483days). At the time of the data-cut off for this analysis, oedema events had resolved in the majority of the subjects (65%, 15/23). The median duration of the events was 23 days (range: 2 to 142 days).

Neutropenia

In the combination treatment group (Cohort B and C) neutropenia events were reported in 14 subjects, in 86% of cases (12/14) were considered treatment-related. One subject each had grade 3 febrile neutropenia and grade 3 pancytopenia. In three subjects (21%) neutropenia events were characterized as serious. None of the events were fatal, and none led to treatment discontinuation, whereas in 11 patients led to dose modifications. The median time to onset of neutropenia events was 62.5 days (range: 21 to 462 days). At the time of the data-cut off for this analysis, the neutropenia events had resolved in majority of the subjects (79%, 11/14). The median duration of neutropenia events was 12 days (range: 7 to 170 days).

Hepatic events

Hepatic events were reported in 12 subjects (15%), and in 83% (10/12) were considered treatment related. Increased blood alkaline phosphatase, increased AST, increased ALT, and increase GGT were reported in more than one subject. Two subjects had grade 3 hepatic events (increased ALT, increased AST, and increased GGT) and one subject had a grade 4 event (increased GGT). In 4 subjects (33%) hepatic events were characterized as serious. None of the events were fatal, and none led to treatment discontinuation, whereas in 8 patients led to dose modifications. Twenty-seven hepatic events were reported in the 12 subjects, with 5 subjects (42%) having three or more occurrences. The median time to onset was 33.5 days (range: 6 to 338 days). At the time of the data-cut off for this analysis, the hepatic events were resolved in 58% (7/12) of these subjects. The median duration of hepatic events was 29 days (range: 6 to 128 days).

Ocular events

Ocular events were reported in 11 subjects (13%), and in 64% (7/11) were considered treatment-related. Visual acuity (in 5 subjects) was the most common preferred term reported. All subjects with the exception of one had grade 1 or 2 events (one subject reported grade 3 visual impairment). In two subjects ocular events were characterized as serious. None of the events were fatal, and none led to treatment discontinuation, whereas in 3 patients led to dose modifications. Sixteen ocular events were reported in the 11 subjects, with 9 subjects (82%) having only one occurrence. The median time to onset of ocular events from the start of combination treatment was 63 days (range: 2 to 254 days). At the time of the data-cut off for this analysis, ocular events had resolved in the majority of these subjects (45%, 5/11). The median duration of the events was 34 days (range: 4 to 73 days), with 83% (5/6) of these subjects having a resolution more than 10 days after the event.

Pancreatitis

Pancreatitis was reported in a total of 3 individuals out of 82 patients. One patient presented a grade 3/4 pancreatitis.

Pneumonitis

One case of pneumonitis was reported

Integrated list of Adverse drug reactions (ADRs)

The safety of trametinib in combination with dabrafenib has been evaluated in the integrated safety population of 641 patients with BRAF V600 mutant unresectable or metastatic melanoma and advanced NSCLC treated with trametinib 2 mg once daily and dabrafenib 150 mg twice daily. Of these patients, 559 were treated with the combination for BRAF V600 mutant melanoma in two randomised Phase III studies, MEK115306 (COMBI-d) and MEK116513 (COMBI-v), and 82 were treated with the combination for BRAF V600 mutant NSCLC in a multi-cohort, non-randomised Phase II study BRF113928.

Table 29. Adverse drug reactions for patients enrolled with Dabrafenib and Trametinib combotherapy in MEK115306, MEK116513, and BRF113928

System organ class	Frequency (all grades)	n	(%)	Adverse reactions
Infections and Infestations	Very common	64	(10)	Urinary tract infection
		88	(14)	Nasopharyngitis
	Common	14	(2)	Cellulitis
		35	(5)	Folliculitis
		14	(2)	Paronychia
		15	(2)	Rash pustular
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	24	(4)	Cutaneous squamous cell carcinoma[a]
		16	(2)	Papilloma[b]
		26	(4)	Seborrhoeic keratosis
	Uncommon	2	(<1)	New primary melanoma
		4	(<1)	Acrochordon (skin tags)
Blood and lymphatic system disorders	Very common	68	(11)	Neutropenia
	Common	53	(8)	Anaemia
		25	(4)	Thrombocytopenia
		28	(4)	Leukopenia
Immune system disorders	Uncommon	5	(<1)	Hypersensitivity[c]
Metabolism and nutrition disorders	Very common	96	(15)	Decreased appetite
	Common	23	(4)	Dehydration
		29	(5)	Hyponatraemia
		25	(4)	Hypophosphataemia
		26	(4)	Hyperglycaemia
Nervous system disorders	Very common	196	(31)	Headache
		84	(13)	Dizziness
Eye disorders	Common	30	(5)	Vision blurred
		14	(2)	Visual impairment
	Uncommon	3	(<1)	Chorioretinopathy
		6	(<1)	Uveitis
		2	(<1)	Retinal detachment
		3	(<1)	Periorbital oedema
Cardiac disorders	Common	54	(8)	Ejection fraction decreased
	Uncommon	5	(<1)	Bradycardia
	Unknown	0	(0)	Myocarditis
Vascular disorders	Very common	162	(25)	Hypertension
		140	(22)	Haemorrhage[d]
	Common	35	(5)	Hypotension
		26	(4)	Lymphoedema
Respiratory, thoracic and mediastinal disorders	Very common	144	(22)	Cough
	Common	58	(9)	Dyspnoea
		7	(1)	Pneumonitis
Gastrointestinal disorders	Very common	76	(12)	Abdominal pain
		97	(15)	Constipation
		213	(33)	Diarrhoea
		239	(37)	Nausea
		190	(30)	Vomiting
	Common	49	(8)	Dry mouth
		14	(2)	Stomatitis
	Uncommon	1	(<1)	Pancreatitis
		3	(<1)	Gastrointestinal perforation[e]
		4	(<1)	Colitis
Skin and subcutaneous disorders	Very common	82	(13)	Dry skin
		74	(12)	Pruritus
		161	(25)	Rash
		64	(10)	Erythema
	Common	45	(7)	Dermatitis acneiform
		26	(4)	Actinic keratosis
		37	(6)	Night sweats
		43	(7)	Hyperkeratosis
		48	(7)	Alopecia
		22	(3)	Palmar-plantar erythrodysaesthesia syndrome
		25	(4)	Skin lesion
		37	(6)	Hyperhidrosis

System organ class	Frequency (all grades)	n	(%)	Adverse reactions
		14	(2)	Panniculitis
		8	(1)	Skin fissures
Musculoskeletal and connective tissue disorders	Very common	165	(26)	Arthralgia
		108	(17)	Myalgia
		84	(13)	Pain in extremity
		66	(10)	Muscle spasms
Renal and urinary disorders	Common	7	(1)	Renal failure
	Uncommon	1	(<1)	Nephritis
General disorders and administration site conditions	Very common	208	(32)	Fatigue
		204	(32)	Chills
		113	(18)	Asthenia
		120	(19)	Oedema peripheral
		361	(56)	Pyrexia
	Common	15	(2)	Mucosal inflammation
		58	(9)	Influenza-like illness
		9	(1)	Face oedema
Investigations	Very common	84	(13)	Alanine aminotransferase increased
		78	(12)	Aspartate aminotransferase increased
	Common	56	(9)	Blood alkaline phosphatase increased
		51	(8)	Gamma-glutamyltransferase increased
		20	(3)	Blood creatine phosphokinase increased

[a] cu SCC: SCC (n=7), SCC of skin (n=6), Bowen's disease (n=7) and keratoacanthoma (n=4)
[b] Papilloma (n=2), skin papilloma (n=14)
[c] Includes drug hypersensitivity (n=2)
[d] Bleeding from various sites, including intracranial bleeding and fatal bleeding
e Includes duodenal perforation (n=1), intestinal perforation (n=1), jejunal perforation (n=1)

Serious adverse event/deaths/other significant events

SAEs

Table 30. Serious adverse events regardless of study drug relationship by preferred term and maximum grade (greater than or equal to 2% for all grades in combination pooled group) in the combination population

	Combination pooled N=82		Combination second-line plus N=57		Combination first-line N=25	
	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any Preferred term	23 (28)	38 (46)	20 (35)	32 (56)	3 (12)	6 (24)
Pyrexia [1]	1 (1)	10 (12)	1 (2)	9 (16)	0	1 (4)
Anaemia	1 (1)	3 (4)	1 (2)	3 (5)	0	0
Alanine aminotransferase increased	1 (1)	2 (2)	1 (2)	1 (2)	0	1 (4)
Aspartate aminotransferase increased	0	2 (2)	0	1 (2)	0	1 (4)
Confusional state	0	2 (2)	0	2 (4)	0	0
Decreased appetite	0	2 (2)	0	2 (4)	0	0
Ejection fraction decreased	0	2 (2)	0	1 (2)	0	1 (4)
Haemoptysis	1 (1)	2 (2)	1 (2)	2 (4)	0	0
Hypercalcaemia	2 (2)	2 (2)	2 (4)	2 (4)	0	0
Nausea	0	2 (2)	0	2 (4)	0	0
Pulmonary embolism	2 (2)	2 (2)	1 (2)	1 (2)	1 (4)	1 (4)
Squamous cell carcinoma of skin	2 (2)	2 (2)	2 (4)	2 (4)	0	0
Vomiting	1 (1)	2 (2)	0	1 (2)	1 (4)	1 (4)

Table 31. Serious adverse events suspected to be study drug related by preferred term and maximum grade (greater than or equal to 2% for all grades in combination pooled group) in the combination population

	Combination pooled N=82		Combination second-line plus N=57		Combination first-line N=25	
	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)
Any Preferred term	11 (13)	23 (28)	11 (19)	19 (33)	0	4 (16)
Pyrexia	1 (1)	9 (11)	1 (2)	8 (14)	0	1 (4)
Alanine aminotransferase increased	1 (1)	2 (2)	1 (2)	1 (2)	0	1 (4)
Anaemia	0	2 (2)	0	2 (4)	0	0
Aspartate aminotransferase increased	0	2 (2)	0	1 (2)	0	1 (4)
Ejection fraction decreased	0	2 (2)	0	1 (2)	0	1 (4)

Deaths

Table 32. Summary of deaths

	Pooled Combination (N=82)	Combination Therapy Second Line (N=57)	Combination Therapy First-Line (N=25)	Monotherapy Second Line (N=84)
Subject Status				
Dead	24 (29%)	23 (40%)	1 (4%)	57 (68%)
Alive at last contact, follow-up ended	2 (2%)	2 (4%)	0	9 (11%)
Alive at last contact, follow-up ongoing	56 (68%)	32 (56%)	24 (96%)	18 (21%)
Primary Cause of Death				
Disease under Study	21 (26%)	20 (35%)	1 (4%)	51 (61%)
SAE possibly related to study treatment	0	0	0	1 (1%)[2]
Other	3 (4%)[1]	3 (5%)[1]	0	5 (6%)[3]
Time to Death From First Dose				
<= 30 Days	2 (2%)	2 (4%)	0	1 (1%)
> 30 Days	22 (27%)	21 (37%)	1 (4%)	56 (67%)
Time to Death From Last Dose				
<= 30 Days	8 (10%)	7 (12%)	1 (4%)	17 (20%)
> 30 Days	16 (20%)	16 (28%)	0	40 (48%)

[1] One patient was captured as "other: progressive disease" for primary cause of death. Two patients died due to SAEs not related to the combination treatment: one patient with retroperitoneal bleeding and one patient with subarachnoid hemorrhage.
[2] Patient died of intracranial hemorrhage - event was suspected to be related to dabrafenib treatment by the Investigator.
[3] Two patients were reported to have been euthanized in the case report form, and both had disease progression as the cause of death in their death certificates. For the remaining three patients, the cause of death was reported as unknown but the outcomes were consistent with disease progression.

Laboratory findings

Laboratory findings of Cohort C have not been submitted due to the short follow up.

In Cohort B, the majority of shifts in haematology and clinical chemistry values were grades 1 or 2, and no clinically meaningful trends in mean values were observed. Frequently reported grade 3 post-baseline values were decreased haemoglobin (6 pts, 11%), decreased lymphocytes (6 pts, 11%), decreased neutrophils (5 pts, 9%), high glucose (6 pts; 11%), high phosphate (3 pts; 5%), and low sodium (7 pts; 13%). Grade 4 increases were reported for decreased leukocytes (1 pt, 2%) and decreased lymphocytes (1 pt, 2%), hypomagnesemia (1 pt; 2%) and hyponatremia (2 pts; 4%). No Hy's law cases were reported.

In Cohort A, the majority of shifts in haematology and clinical chemistry values were grades 1 or 2, and no clinically meaningful trends in mean values were observed. Post-baseline grade 3 values were decreased lymphocytes (6 pts, 7%), glucose high (7 pts, 9%), phosphate (4 pts, 5%), and potassium low (2 pts, 3%). One patient (1%) had grade 4 post-baseline increased glucose and 1 patient (1%) had grade 4 low magnesium. One patient (1%) had both grade 3 post-baseline increased alanine aminotransferase (ALT) and grade 4 increased aspartate aminotransferase (AST) values. No Hy's law cases were observed.

ECG

In Cohort B, of the 55 evaluated patients, 7 subjects (13%) had an increased QTc of 31-60 msec and 1 patient (2%) had QTc increased >60 msec post-baseline. None of the patients had grade 3 shifts in QTc post-baseline (>= 501 msec), 5 subjects had post-baseline increase to grade 2 (481 to 500 msec) and 10 subjects had a post-baseline increase to grade 1 (450 to 480 msec). Most of these QTcF increases were observed within the Week 24 assessment visit. For all subjects with the exception of one, the post-baseline changes in ECG findings were assessed to be not significant clinically.

LVEF

In Cohort B, of the 50 evaluated patients, 78% had any post-baseline decrease in LVEF, with 0-10% decrease observed in 52% of these subjects. Three patients (6%) met the specific protocol-mandated criteria requiring dose interruption (LVEF was >10% below baseline and below the institutional LLN), which was reported as an SAE.

In the integrated safety population of trametinib in combination with dabrafenib, decreased LVEF has been reported in 8% (54/641) of patients

Safety in special populations

Age

In second-line plus population (Cohort B), the median duration on combination treatment was similar for subjects < 65 and ⩾ 65 years (10.6 months vs 10.3 months). Adverse event profile as well as the incidence of grade 3-4 AEs was similar between the subjects < 65 and ⩾ 65 years of age (48% and 50%, respectively). The AEs that were more frequently reported in the younger subjects compared to the older subjects (with a ⩾ 10% difference) are: pyrexia, cough, peripheral oedema, arthralgia, dyspnoea, blood alkaline phosphatase increased, back pain, headache, hyperkeratosis, nasopharyngitis, alopecia, folliculitis, conjunctivitis, eczema, hair texture abnormal, hyperhidrosis, and malaise. The following AEs were more frequently reported in the older subjects compared to the younger subjects (with a ⩾ 10% difference) are: dry skin, dry mouth, and constipation.

In the integrated safety population of trametinib in combination with dabrafenib (n=641) 180 patients (28%) were ⩾65 years of age; 50 patients (8%) were ⩾75 years of age.

Gender

In Cohort B, the median duration on combination treatment was slightly higher for male subjects than female subjects (10.7 months vs 9.1 months). Male subjects had more AEs requiring dose reduction (41% vs 29%) and dose interruptions (69% vs 54%) and grade 3-4 AEs (55% vs 43%). In contrast, more female subjects had fatal SAEs (11% vs 3%) and death events (15 pts (26%) and 8 pts (14%), respectively). The following AEs were reported more frequently (⩾10% difference) in male subjects than female subjects: pyrexia, chills, weight decreased, increased blood alkaline phosphatase, chest pain, productive cough, weight increased, increased blood creatinine, haemoptysis, confusional state, dehydration, and pneumonia. The following AEs were reported more frequently in the female subjects than male subjects (⩾10% difference subjects): diarrhoea, arthralgia, neutropenia, peripheral oedema, constipation, back pain, headache, myalgia, alopecia, dyspepsia, rhinitis, and urinary tract infection.

Race

The safety profile of the dabrafenib and trametinib combination by race cannot be compared in Cohort B due to the small sample size of Asians (4 pts) and African Americans (2 pts).

Safety related to drug-drug interactions and other interactions

No new clinically relevant drug-drug interaction signal has been identified in the data submitted to support this application.

Discontinuation due to adverse events

Dose Reductions

Table 33. Adverse events leading to dose reduction regardless of study drug relationship by preferred term and maximum grade in the combination population

	Combination pooled N=82		Combination second-line plus N=57		Combination first-line N=25	
	Grade 3/4 N (%)	All grades N (%)	Grade 3/4 N (%)	All grades N (%)	Grade 3/4 N (%)	All grades N (%)
Any Preferred term	**10 (12)**	**24 (29)**	**9 (16)**	**20 (35)**	**1 (4)**	**4 (16)**
Pyrexia	1 (1)	7 (9)	1 (2)	6 (11)	0	1 (4)
Diarrhoea	1 (1)	3 (4)	1 (2)	3 (5)	0	0
Neutropenia	3 (4)	3 (4)	2 (4)	2 (4)	1 (4)	1 (4)
Alanine aminotransferase increased	1 (1)	2 (2)	1 (2)	1 (2)	0	1 (4)
Blood creatinine increased	0	2 (2)	0	2 (4)	0	0
Nausea	0	2 (2)	0	2 (4)	0	0
Abdominal pain	0	1 (1)	0	0	0	1 (4)
Amylase increased	1 (1)	1 (1)	1 (2)	1 (2)	0	0
Aspartate aminotransferase increased	0	1 (1)	0	0	0	1 (4)
Blood alkaline phosphatase increased	0	1 (1)	0	1 (2)	0	0
Chills	0	1 (1)	0	1 (2)	0	0
Cholecystitis acute	1 (1)	1 (1)	1 (2)	1 (2)	0	0
Decreased appetite	0	1 (1)	0	1 (2)	0	0
Ejection fraction decreased	0	1 (1)	0	1 (2)	0	0
Erythema nodosum	0	1 (1)	0	0	0	1 (4)
Gamma-glutamyltransferase increased	1 (1)	1 (1)	1 (2)	1 (2)	0	0
Glomerulonephritis chronic	0	1 (1)	0	1 (2)	0	0
Hypotension	0	1 (1)	0	1 (2)	0	0
Inflammation	0	1 (1)	0	1 (2)	0	0
Leukopenia	0	1 (1)	0	1 (2)	0	0
Malaise	0	1 (1)	0	1 (2)	0	0
Pancreatitis acute	0	1 (1)	0	1 (2)	0	0
Sinus tachycardia	0	1 (1)	0	1 (2)	0	0
Tubulointerstitial nephritis	1 (1)	1 (1)	1 (2)	1 (2)	0	0
Vomiting	0	1 (1)	0	1 (2)	0	0

Dose Interruptions

Adverse events leading to dose interruption were reported in 35 patients (61%). Of these, 17 patients (30%) had grade 3 and three patients (5%) had grade 4 AEs.

The frequently reported (occurring in ≥ 5% of patients) AEs leading to dose interruptions were: pyrexia, neutropenia, vomiting, chills, blood creatinine increased, and nausea. The incidence of grade 4 AEs requiring dose interruptions was low (3 patients; 5%), and consisted of gamma-glutamyltransferase increased, hyponatraemia, legionella infection (each reported in 1 patient)

2.6.1. Discussion on clinical safety

The combination of dabrafenib and trametinib has already been investigated in the context of procedure WS-0736 which extended the indication of both individual products to the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Pyrexia was the most common AE in the combination therapy arms and this adverse event occurred in approximately one half of the patients receiving combination therapy in both studies (see sections 4.4 and 4.8 of the SmPC).

Nausea, chills and diarrhoea also occurred in ≥30% of the patients in the combination therapy arm of both MEK115306 and MEK116513 with comparable incidences. ADRs that required special warning in the SmPC were new malignancies (cutaneous squamous cell carcinomas, new primary melanoma, non-cutaneous malignancies), haemorrhage, LVEF reduction/left ventricular dysfunction, pyrexia, deep vein thrombosis/pulmonary embolism (DVT/PE), hypertension, visual impairment, rash, rhabdomyolysis, renal failure, pancreatitis and hepatic events (see section 4.4 and 4.8 of the SmPC).

cuSCC was reported more frequently in the BRAF inhibitor monotherapy arms than in the combination therapy arms (4-10% for dabrafenib monotherapy and vemurafenib monotherapy vs <1% for the combination therapy). The incidence of Grade 3 events for rash, cuSCC and keratoacanthoma was also lower in the combination therapy arms in comparison to monotherapy arms (rash 0-15 vs 2-13%, squamous cell carcinoma 1 vs 5-10%, keratoacanthoma 1 vs 2-9%).

Overall, the safety profile of dabrafenib (Tafinlar) in combination with trametinib (Mekinist) in patients with advanced NSCLC harbouring a BRAFV600 mutation appears in line with the safety aspects known for the indication of the combination in advanced BRAF V600 mutant melanoma. However, data in NSCLC are challenged by the relatively limited number of patients treated (82 patients) and the relatively short follow-up. Of note, the combination first line treatment group (Cohort C) of the BRF113928 study included only 25 patients with median duration of treatment of only 2.73 months.

In the dabrafenib monotherapy group of the BRF113928 study (Cohort A, n=84) the most frequently reported treatment-related AEs (in $\geqslant$ 20% of patients) were hyperkeratosis (27%), nausea (25%), skin papilloma (24%), dry skin (23%), pyrexia (21%), asthenia (21%), and palmar-plantar erythrodysaesthesia syndrome (20%). Most of events were mild or moderate in severity (grade 1-2); 32% of patients had grade 3 events (essentially CuSCC (10%), BCC (7%), asthenia (6%)), whereas grade 4 and 5 AEs were reported in one patient each (grade 4 hyperglycaemia and grade 5 intracranial haemorrhage). A total of 36 patients (43%) had SAEs, with the most commonly reported SAEs occurring in $\geqslant$ 2% of patients being CuSCC (10%), pyrexia (6%), basal cell carcinoma (5%), ejection fraction decreased (2%), pneumonia (2%), and respiratory tract infection (2%). One patient died due to a SAE of intracranial haemorrhage considered treatment related by the investigator.

In the dabrafenib-trametinib second line plus combination group of the BRF113928 study (n=82, Cohort B) the most frequently reported treatment-related AEs (in $\geqslant$ 20% of patients) were pyrexia (42%), nausea (35%), vomiting (26%), diarrhoea (23%), and dry skin (23%). Most of events were mild or moderate in severity (grade 1-2); 32% of patients had grade 3-4 events. The most common grade 3 AEs reported in >2% of patients was neutropenia (9%) and leukopenia (4%). All other grade 3 AEs occurred at an incidence of $\leqslant$ 2%. Four patients experienced grade 4 AEs (anaemia, hyponatremia, gamma-glutamyltransferase increased, and legionella infection). A total of 38 patients (46%) experienced at least one SAE regardless of relationship to the study treatment: 32 patients (56%) in Cohort B and 6 patients (24%) in Cohort C. However, no fatal related SAE were observed. AESI were frequently observed but usually were of grade 1-2 severity and manageable with dose modifications and/or treatment interruptions.

In the dabrafenib-trametinib combination first line group (Cohort C, n=25) AEs were similar to the ones reported in Cohort B. However, the incidence of AEs and AESIs was generally lower in Cohort C, probably due to the short follow up and the very limited number of patients treated.

QT-prolongation has previously been assessed in a dedicated study without specific findings. In the NSCLC studies there was a single patient with major confounding factors with *per se* relevant prolongation. Information in section 5.1 of the SmPC is considered adequate. The Applicant also took the opportunity to reflect in sections 4.2 and 4.4 of the SmPC of trametinib, changes related to QT prolongation that were implemented during variation EMEA/H/C/002604/II/0019.

Intracranial hemorrhages have been reported in 6 patients in the melanoma studies, all with confounding factors. There were no reports in the NSCLC studies, but this adverse reaction remains listed in section 4.8 of the SmPC and covered by the warning regarding hemorrhage in section 4.4.

The safety profile of the dabrafenib-trametinib combination compares favourably to the known safety profile of the platinum-based doublet chemotherapy where patients experience ≥ grade 3 events in more than 85% of patients with the most common ⩾ grade 3 adverse events being neutropenia (>60%), nausea (9 to 37%), vomiting (8 to 35%) (Schiller JH. et al, 2002).

2.6.2. Conclusions on clinical safety

The safety profile of the combination treatment in NSCLC is similar to what has been observed for the melanoma indication. ADRs are considered manageable when following the recommendations in the SmPCs.

Potential differences in safety of the dabrafenib/trametinib combination would be related to the indication for use. In lung cancer for example there is usually an increased risk for bleeding. This has not been observed in the submitted data however BRAF V600 positive lung cancer is almost exclusively seen in non-squamous histology where the risk is lower than in squamous cell carcinoma.

PSUR cycle

The PSUR cycle remains unchanged.

2.7. Risk management plan

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

The PRAC considered that the risk management plan version 13.1 for Mekinist (trametinib) is acceptable.

The PRAC considered that the risk management plan version 8.2 for Tafinlar (dabrafenib) could be acceptable if the applicant implements the changes to the RMP as described in the CHMP/PRAC Rapporteur assessment report. Before the adoption of the opinion the MAH provided an updated RMP (v8.3) which was found acceptable by the PRAC rapporteur.

The joint CHMP/PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plans version 13.1 for Mekinist (trametinib) and version 8.3 for Tafinlar (dabrafenib) with the following content:

Safety concerns

Mekinist (trametinib)

Summary of the Safety Concerns (changes appear in red italic)

Important identified risks	• Skin toxicities (e.g., rash, dermatitis acneiform) • Left ventricular systolic dysfunction (e.g., LVEF decreased and left ventricular dysfunction) • Ocular events (e.g., retinal vein occlusion, retinal pigment epithelial detachment)

	• Pneumonitis/Interstitial lung disease • Hepatic events (e.g., AST, ALT increased *and hepatic failure*) • Hypertension • Hypersensitivity • Rhabdomyolysis • Hemorrhagic events • *Gastrointestinal disorders (diarrhea, colitis, and GI perforation)*
Important identified risks related to trametinib+dabrafenib combination therapy only	• Neutropenia
Important potential risks	• Off-label use: in resectable/resected melanoma (adjuvant *therapy)/NSCLC*, in non-melanoma/*non-NSCLC* tumours harbouring a BRAF V600-mutation, melanoma/*NSCLC* tumours negative for BRAF V600-mutation, in patients with tumour progression during prior treatment with BRAF inhibitor therapy (trametinib monotherapy only), in combination with other anti-cancer agents, or when non-validated tests are used • ~~Hepatic failure~~ • Impaired female fertility • Developmental toxicity • Use in elderly population (≥65 years old) • Safety in children <18 years old (including potential adverse effects on skeletal maturation and sexual maturation)
Important potential risks related to trametinib+dabrafenib combination therapy only	• Pulmonary embolism, deep vein thrombosis
Missing information	• Use in patients with reduced cardiac function or symptomatic Class II, III, or IV heart failure (NYHA functional classification system) • Safety in patients with severe renal impairment • Safety in patients with moderate to severe hepatic impairment • Use in Non-White population • Pregnancy and risks in breast-feeding • Safety in patients with recent (within 6 months) acute coronary syndrome including unstable angina, coronary angioplasty, stenting or cardiac arrhythmias (except sinus arrhythmia) and treatment refractory hypertension (blood pressure of systolic >140 mmHg and/or diastolic >90 mmHg which cannot be controlled by anti-hypertensive therapy) • Safety in patients with history of retinal vein occlusion or central serous retinopathy (reclassified as Retinal Pigment Epithelial Detachment, RPED) • Safety in patients with history of pneumonitis or interstitial lung disease • Drug-drug interactions (~~*hepatobiliary elimination*~~ *effect* of trametinib *on oral contraceptives* ~~*and P-gp inhibition*~~)

The proposed changes are not based on new data submitted within this variation but were follow-up actions from EMEA/H/C/PSUSA/0010262/201505 and EMEA/H/C/PSUSA/0010262/201511.

Tafinlar (dabrafenib)

Summary of the Safety Concerns (changes appear in red italic)

Important identified risks	• *Cutaneous SCC~~cuSCC~~* • New primary melanoma • Non-cutaneous secondary/recurrent malignancies • Pre-renal and Intrinsic Renal failure • Pancreatitis • Uveitis • *Medicinal Products that are sensitive substrates of CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19, UDP glucuronosyl transferase (UGT) and transporters. Medicinal Products that are strong inhibitors of CYP3A4 and CYP2C8*
Important identified risks related to trametinib+dabrafenib combination therapy only	• Neutropenia • ~~*Gastrointestinal disorders (diarrhea, colitis, and GI perforation)*~~
Important potential risks	• Non-specific cardiac toxicity • Testicular toxicity • Drug-drug interactions*(strong CYP3A4 and CYP2C8 inducers, pH-altering agent and OATP1B1/3 substrate)* • Developmental toxicity • Photosensitivity
Important potential risks related to trametinib+dabrafenib combination therapy only	• Pulmonary embolism, deep vein thrombosis
Missing information	• Use in patients with reduced cardiac function or symptomatic Class II, III, or IV heart failure (NYHA functional classification system) • Safety in patients with severe renal impairment • Safety in patients with moderate to severe hepatic impairment • Use in Non-White population • Pregnancy and risks in breast-feeding • Use in patients with baseline QTc ≥480 msec; history of acute coronary syndrome (including unstable angina), coronary angioplasty, stenting, or cardiac arrhythmias (except sinus arrhythmia) within the past 24 weeks; and abnormal cardiac valve morphology (moderately abnormal or worse)

Gastrointestinal disorder is a new important identified risk that applies to trametinib monotherapy and trametinib in combination with dabrafenib only. This risk is not applicable to dabrafenib monotherapy. Since only those safety concerns associated with "combination therapy only" (not with monotherapy) should be listed in this part the MAH was asked to remove "Gastrointestinal disorders (diarrhoea, colitis, and GI perforation)" from the Important identified risks related to trametinib+dabrafenib combination therapy only.

The safety concern "Drug-Drug interactions" was further specified between what is considered as an identified risk and what is considered as a potential risk.

Pharmacovigilance plan

Summary of planned additional PhV activities from RMP

Mekinist (trametinib)

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final Reports** (planned or actual)
Study MEC116354 Hepatic Impairment NCI Sponsored Phase I and PK Study (Clinical, 3)	NCI Sponsored Phase I and PK Study to obtain dosing recommendation in patients with hepatic impairment	Safety in patients with moderate to severe hepatic impairment	Study started	Final report projected in ~~*4Q2017*~~ *4Q2018*
Study 201711 Annual Reports for Cardiomyopathy-related adverse reactions (Clinical, 3)	Cumulative safety analyses will be submitted (abbreviated)	Cumulative annual safety analyses of Left ventricular systolic dysfunction	Study started	Final report projected in 4Q2020
BRF115532 (COMBI-AD) Phase III Adjuvant Study (Clinical, 3)	A phase III randomized double blind study of dabrafenib in COMBInation with trametinib versus two placebos in the ADjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection	Long-term safety with focus on non-cutaneous malignancies and haemorrhagic events	Study started	Primary study report projected ~~*1Q2018*~~ *1Q2019*
Study BRF117277 Phase II Brain Metastases Study (Clinical, 3)	Phase II, Open Label study of Dabrafenib plus Trametinib in subjects with BRAF mutation positive Melanoma that has metastasized to the brain	Safety in patients with brain metastases with focus on haemorrhagic events	Study started	Final report complete 4Q2017
Trametinib PIP: EMEA-001177-PIP01-11 Study MEK116540 (Clinical, 3)	To understand and collect information regarding use and safety of trametinib in children and adolescents	Safety in children <18 years old (including potential adverse effects on skeletal maturation and sexual maturation)	Study started	Final report projected 3Q2018
Study MEK113707 *A study to determine whether there is a*	*To assess the effect of repeat-dose trametinib on*	*Drug-drug interaction*	*Planned*	~~*2Q2018*~~*4Q2019*

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final Reports** (planned or actual)
potential for drug interaction between trametinib and certain types of hormonal birth control (oral contraceptives)	*the repeat-dose pharmacokinetics of certain types of hormonal birth control (ethinyl estradiol and norethindrone).*			

Tafinlar (dabrafenib)

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final Reports** (planned or actual)
200919: In vivo interaction study with an OATP1B1/3 substrate (clinical, 3)	To evaluate the effect of single and repeat dose dabrafenib on the single dose pharmacokinetics of an OATP1B1/1B3 substrate such as rosuvastatin and of CYP3A4 substrate midazolam	Drug-drug interactions*(strong CYP3A4 and CYP2C8 inducers, pH-altering agent and OATP1B1/3 substrate)*	Ongoing	Final report projected in 3Q2017
BRF115532 (COMBI-AD) Phase III Adjuvant Study (Clinical, 3)	A phase III randomized double blind study of dabrafenib in COMBInation with trametinib versus two placebos in the ADjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection	Non-cutaneous secondary/recurrent malignancies and hemorrhagic events	Ongoing	Primary study report projected ~~*1Q2018*~~ *1Q2019*
~~*RAD*~~*200072:* Drug-drug interaction study of the effects of a strong CYP3A4 inducer (e.g., rifampin) and a pH-altering agent (e.g., proton pump inhibitor) on dabrafenib (Clinical, 3)	To evaluate the effect of repeat dose of rifampin, a strong CYP3A4 inducer, and of a pH altering agent (i.e., proton pump inhibitor) on the repeat dose pharmacokinetics of dabrafenib.	Drug-drug interactions*(strong CYP3A4 and CYP2C8 inducers, pH-altering agent and OATP1B1/3 substrate)*	Ongoing	Final report ~~*2Q2017*~~ *1Q2017*
BRF113683 (BREAK-3) (Clinical, 3)	A Phase III randomized, open-label study comparing dabrafenib to DTIC in previously untreated subjects with BRAF mutation positive advanced (Stage III) or metastatic (Stage IV) melanoma.	Non-cutaneous secondary/recurrent malignancies	Ongoing	Final report projected ~~*1Q2017*~~ *3Q2017*
BRA115947 ~~*Hepatic and Renal Impairment*~~ (CDRB436DUS04T)	Hepatic ~~*NCI Sponsored Phase I*~~ and ~~*PK Study to obtain dosing recommendation in patients with*~~	*Hepatic and renal impairment*	Stopped	Final report projected *1Q2017*

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final Reports** (planned or actual)
(Clinical, 3)	~~*severe*~~ renal ~~*or moderate to severe hepatic*~~ impairment	~~*Pre-renal and Intrinsic Renal failure and Hepatic events (e.g., AST, ALT, increased)*~~		
CDRB436A2106	A phase I, open label, multicenter, single dose study to evaluate the pharmacokinetics of dabrafenib in healthy subjects with normal renal function and subjects with impaired renal function	Severe renal impairment	Planned	Final report ~~*Dec 2019*~~ *1Q2020*
CDRB436A2107	A phase I, open label, multicenter, single dose study to evaluate the pharmacokinetics of dabrafenib in healthy subjects with normal hepatic function and subjects with impaired hepatic function	Moderate and severe hepatic impairment	Planned	Final report ~~*Dec 2019*~~ *1Q2020*
201710 Secondary malignancies (clinical; 3)	A non-interventional study to perform evaluation of secondary malignancies in patients treated with dabrafenib in randomized, controlled trials	Non-cutaneous secondary/recurrent malignancies	Ongoing	Final report projected in 4Q2020

There are no new studies proposed in the pharmacovigilance plan for either Mekinist or Tafinlar. MEK113707 (drug-drug interaction study) for Mekinist, a legacy study from the previous MAH, has now been included as an additional pharmacovigilance activity for the important potential risk "drug-drug interactions".

Furthermore the MAH has updated date of submission of final reports for several studies which is found acceptable.

The proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Mekinist (trametinib)

Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**
Important identified trametinib risks		
Skin toxicities (e.g., Rash, Dermatitis acneiform)	This item is appropriately communicated through current labeling. Relevant terms are included as ADRs in SmPC	None.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	(Section 4.8 Undesirable effects).	
Left Ventricular Systolic Dysfunction (e.g., LVEF decreased and left ventricular dysfunction)	This item is appropriately communicated through current labeling. Relevant terms are included as ADRs in SmPC (Section 4.8 Undesirable effects).	None
Ocular events (e.g., retinal vein occlusion, retinal pigment epithelial detachment)	This item is appropriately communicated through current labeling. Relevant terms are included as ADRs in SmPC (Section 4.8 Undesirable effects).	None.
Pneumonitis/Interstitial lung disease	This item is appropriately communicated through current labeling. Relevant terms are included as ADRs in SmPC (Section 4.8 Undesirable effects).	None.
Hepatic events (e.g., AST and ALT increased, *and hepatic failure)*	This item is appropriately communicated through current labeling. Relevant terms are included as ADRs in SmPC (Section 4.8 Undesirable effects).	None.
Hypertension	This item is appropriately communicated through current labeling. Relevant terms are included as ADRs in SmPC (Section 4.8 Undesirable effects).	None.
Hypersensitivity	This item is appropriately communicated through current labeling. Relevant terms are included as ADRs in SmPC (Section 4.8 Undesirable effects).	None.
Rhabdomyolysis	This item is appropriately communicated through current labeling. Relevant terms are included as ADRs in SmPC (Section 4.8 Undesirable effects).	None.
Hemorrhagic events	This item is appropriately communicated through current labeling. Relevant terms are included as ADRs in SmPC (Section 4.8 Undesirable effects).	None.
Gastrointestinal disorders (diarrhea, colitis, and GI perforation)	This item is appropriately communicated through current labeling: SmPC Section 4.4 Special warnings and	None.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	precautions for use and in Section 5.3 Preclinical safety data. Relevant terms are included as ADRs in SmPC (Section 4.8 Undesirable effects).	
Important identified risks related to trametinib and dabrafenib combination therapy only		
Neutropenia	This item is appropriately communicated through current labeling: Relevant terms are included as ADRs in SmPC (Section 4.8 Undesirable effects).	None.
Important potential risks		
Off-label use in resectable/resected melanoma (adjuvant therapy)/NSCLC, in non-melanoma/non-NSCLC tumours harbouring a BRAF V600-mutation, melanoma/NSCLC tumours negative for BRAF V600-mutation, in patients with tumour progression during prior treatment with BRAF inhibitor therapy (trametinib monotherapy only), in combination with other anti-cancer agents, or when non-validated tests are used	None.	None.
~~*Hepatic failure*~~	~~*This item is appropriately communicated through current labeling: SmPC Section 4.4 Special warnings and precautions for use.*~~	~~*None.*~~
Impaired female fertility	This item is appropriately communicated through current labeling: SmPC Section 4.4 Special warnings and precautions for use.	None.
Developmental toxicity	This item is appropriately communicated through current labeling: SmPC Section 4.4 Special warnings and precautions for use.	None.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Use in elderly population (≥ 65 years old)	This item is appropriately communicated through current labeling: SmPC Section 4.4 Special warnings and precautions for use.	None.
Safety in children <18 years old (including potential adverse effects on skeletal maturation and sexual maturation)	This item is appropriately communicated through current labeling: SmPC Section 4.2 Posology and method of administration.	None.
Important potential risks related to trametinib + dabrafenib combination therapy only		
Pulmonary embolism, deep vein thrombosis	This item is appropriately communicated through current labeling: SmPC Section 4.4 Special warnings and precautions for use.	None.
Missing information		
Use in patients with reduced cardiac function or symptomatic Class II, III, or IV heart failure (NYHA functional classification system)	This item is appropriately communicated through current labeling: SmPC Section 4.4 Special warnings and precautions for use.	None.
Safety in patients with severe renal impairment	This item is appropriately communicated through current labeling: SmPC Section 4.2 Posology and method of administration.	None.
Safety in patients with moderate to severe hepatic impairment	This item is appropriately communicated through current labeling: SmPC Section 4.2 Posology and method of administration.	None.
Use in Non-White population	This item is appropriately communicated through current labeling: SmPC Section 4.2 Posology and method of administration.	None.
Pregnancy and risks in breast-feeding	This item is appropriately communicated through current labeling: SmPC Section 4.6 Fertility, pregnancy and lactation.	None.
Safety in patients with recent (within 6 months) acute coronary syndrome including unstable angina, coronary angioplasty, stenting or cardiac	This item is appropriately communicated through current labeling: SmPC Section 4.2 Posology and method of administration.	None.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
arrhythmias (except sinus arrhythmia) and treatment refractory hypertension (blood pressure of systolic >140 mmHg and/or diastolic >90 mmHg which cannot be controlled by anti-hypertensive therapy		
Safety in patients with history of retinal vein occlusion or central serous retinopathy (reclassified as Retinal Pigment Epithelial Detachment, RPED)	This item is appropriately communicated through current labeling: SmPC Section 4.2 Posology and method of administration.	None.
Safety in patients with history of pneumonitis or interstitial lung disease	This item is appropriately communicated through current labeling: SmPC Section 4.2 Posology and method of administration.	None.
Drug-drug interactions (~~*hepatobiliary elimination*~~ *effect* of trametinib ~~*and P-gp inhibition on oral*~~ *contraceptives*)	This item is appropriately communicated through current labeling: SmPC Section 4.~~5~~*6* Interaction with other medicinal products and other forms of interaction	None.

Tafinlar (dabrafenib)

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important identified dabrafenib monotherapy risks (including combination therapy)		
cuSCC	• Dose modifications in Section 4.2 of the SmPC • Undesirable effects in Section 4.8 of the SmPC	None
New primary melanoma	• Dose modifications in Section 4.2 of the SmPC • Undesirable effects in Section 4.8 of the SmPC	None
Non-cutaneous secondary/recurrent malignancies	• Dose modifications in Section 4.2 of the SmPC • Undesirable effects in Section 4.8 of the SmPC	None
Pre-renal and intrinsic Renal failure	• Dose modifications in Section 4.2 of the SmPC • Undesirable effects in Section 4.8 of the SmPC	None
Pancreatitis	• Dose modifications in Section 4.2 of the SmPC • Undesirable effects in Section 4.8 of the SmPC	None
Uveitis	• Dose modifications in Section 4.2 of the SmPC • Undesirable effects in Section 4.8 of the SmPC	None
Medicinal Products that are sensitive substrates of CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19, UDP	• *Interactions with other medicinal products and other forms of interactions in Section 4.5 of the SmPC*	*None*

Safety concern	Routine risk minimization measures	Additional risk minimization measures
glucuronosyl transferase (UGT) and transporters. Medicinal Products that are strong inhibitors of CYP3A4 and CYP2C8		
Important identified risks related to dabrafenib and trametinib combination therapy only		
Neutropenia	• Undesirable effects in Section 4.8 of the SmPC	None
~~*Gastrointestinal disorders (diarrhea, colitis, and GI perforation)*~~	• ~~*Warnings and precautions in Section 4.4 of the Mekinist SmPC*~~ • ~~*Undesirable effects in Section 4.8 of the Mekinist SmPC*~~ • ~~*Preclinical safety data in Section 5.3 of the Tafinlar and Mekinist SmPCs*~~	~~*None*~~
Important potential dabrafenib risks (monotherapy only)		
Non-specific cardiac toxicity	• None	None
Testicular Toxicity	• Preclinical safety data in Section 5.3 of the SmPC	None
Drug-drug *interactions (strong CYP3A4 and CYP2C8 inducers, pH-altering agent and OATP1B1/3 substrate)*	• Interactions with other medicinal products and other forms of interactions in Section 4.5 of the SmPC	None
Developmental toxicity	• Fertility, pregnancy and lactation in Section 4.6 of the SmPC • Preclinical safety data in Section 5.3 of the SmPC	None
Photosensitivity	• None	None
Important potential risks related to dabrafenib and trametinib combination only		
Pulmonary embolism, deep vein thrombosis	• Dose modifications in Section 4.2 of the SmPC • Undesirable effects in Section 4.8 of the SmPC	None
Missing information for dabrafenib monotherapy only		
Use in patients with reduced cardiac function or symptomatic NYHA Class II, III, or IV heart failure (NYHA functional classification system)	• Undesirable effects in Section 4.8 of the SmPC	None
Safety in patients with severe renal impairment	• Posology and method of administration in Section 4.2 of the SmPC • Pharmacokinetic properties in Section 5.2 of the SmPC	None
Safety in patients with moderate to severe hepatic impairment	• Posology and method of administration in Section 4.2 of the SmPC • Pharmacokinetic properties in Section 5.2 of the SmPC	None
Non-White population	• None	None
Pregnancy and risks in breast-feeding	• Fertility, pregnancy and lactation in Section 4.6 of the SmPC	None
Use in patients with baseline QTc ≥480 msec; history of acute coronary syndrome (including unstable angina), coronary angioplasty, stenting, or cardiac arrhythmias (except sinus arrhythmia) within the past 24	• None	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
weeks; and abnormal cardiac valve morphology (moderately abnormal or worse)		

The proposed risk minimisation measures for both Mekinist (trametinib) and (Tafinlar) dabrafenib remain sufficient to minimise the risks of the products in the proposed indication.

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the Mekinist SmPC and sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the Tafinlar SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the Mekinist and Tafinlar Product Information to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed and accepted by the CHMP.

2.8.1. User consultation

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

3. Benefit-Risk Balance

Trametinib in combination with dabrafenib is currently authorised for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

BRAF mutations occur in a low frequency (about 2%) in NSCLC, essentially in case of adenocarcinoma or mixed histologies. The V600 mutations are the most commonly encountered mutation in BRAF, encompassing more than half of the BRAF mutations, and act as driving mutations for the proliferation of the tumour and malignancy of the disease.

Historical data indicate that the expected ORR to chemotherapy is low, about 20%, also in case of V600 driven NSCLC. Therefore due to the expected low activity of chemotherapy, the well documented efficacy of dabrafenib and trametinib in BRAF V600 driven melanoma, the genetic link between BRAF V600 NSCLC and the small target population, the MAH decided to conduct three single arm trials: the first cohort enrolled treatment experienced patients and patients were treated with dabrafenib in monotherapy, followed by previously treated administered combination therapy and finally combination therapy in treatment naïve subjects.

3.1. Favourable effects

In the Combination treatment with dabrafenib + trametinib in the second line and beyond setting, the confirmed ORR was 63.2% per IRC assessment (95% CI 49.3; 75.6%). Similar response rates were demonstrated in the first-line setting, 61.1% (95% CI 43.5; 76.9%).

About 80% of responses were observed at first imaging, i.e. at 6 weeks, thus early symptom relief is expected. Median duration of response for the combination 2nd line plus population was found to be 12.6 months (IRC). Prolonged duration of response, as in this case, is associated with delayed progression in symptoms.

The historical ORR to chemotherapy was about 20% for second-line therapies.

Due to the rarity of the condition, experience from melanoma studies and available response data in BRAF V600 mutated NSCLC, the results are accepted as sufficiently convincing to conclude that combination therapy is efficacious in the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation.

3.2. Uncertainties and limitations about favourable effects

The absence of control doesn't allow direct comparison with standard treatment, in particular regarding PFS and OS. However on the basis of the high activity in terms of ORR and duration of response, and indirect comparisons, it is possible to conclude that efficacy has been established.

Only patients with BRAF V600E mutation were enrolled in the studies. Extrapolation to other BRAF V600 mutations was discussed in some detail in relation to the melanoma indication and was considered acceptable with the inclusion of further information in section 5.1 of the SmPC.

3.3. Unfavourable effects

The safety profile is similar in melanoma and NSCLC despite demographic differences. The discontinuation rate was about 14% after a median duration of therapy of about 10 months, but dose interruptions/reductions (60%/35%) are frequent. From a tolerability perspective these rates are considered compatible with a moderate patient impact.

Among SAEs, pyrexia is the most commonly encountered event 10-15%. Combination therapy reduces the incidence of newly detected squamous cancer of the skin, but vigilance is indicated (see sections 4.4 and 4.8 of the SmPC).

The most common adverse reactions (>20%) for the pooled dabrafenib and trametinib combination therapy include pyrexia (45%), nausea (41%), vomiting (30%), diarrhoea (28%), decreased appetite (26%), asthenia (23%), dry skin (23%) and oedema peripheral (23%).

3.4. Uncertainties and limitations about unfavourable effects

The safety evaluation of the combination dabrafenib-trametinib in the BRAF V600 positive NSCLC population is challenged by the limited number of patients treated and the relatively short follow-up. The safety assessment largely relies on the confirmatory studies undertaken in melanoma, but the number of patients in these studies is still less than 600. Safety evaluation is also complemented by routine pharmacovigilance activities.

3.5. Effects Table

Table 34. Effects Table for combination therapy (dabrafenib + trametinib)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
Favourable Effects					
ORR 2nd line+	Confirmed response RECIST1.1 (IRC)	% 95% CI	63% (49; 76%)	Historical control in patients with BRAFV600E mutation. ICFT study: ORR in 2nd line 21% (95%CI: 9.8; 31.7) ORR 1st line 30.3% (95% CI: 21.6, 38.9) and OS of 15.2 months when excluding those treated with BRAF inhibitor.	Convincingly high
ORR 1st line	Confirmed response RECIST1.1 (IRC)	% 95% CI	61% (44; 77%)		
DOR 2nd line+	Median	m.	13		
Unfavourable Effects					
Study discontinuation 2nd line+			14%		Exclude first-line update
Dose reduction 2nd line+			35%		
SAE related			33%		In the 2 melanoma combination studies, SAE were reported in 42% and 37%. Pyrexia was reported as SAE in 14% and 17% of patients. Any grade 3 events were reported in 40% and 48% of patients and any grade 4 events were reported in 5% of patients. Using CT historical control, grade ⩾ 3 events reported in more than 85% of patients. Most common grade ⩾ 3 AE being neutropenia (>60%), nausea (9 to 37%), vomiting (8 to 35%) (Schiller JH. et al, 2002)
SAE	Pyrexia		14%		
Any grade 3			42%		
Any grade 4			7%		

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Given the high level of ORR reported for combination therapy (60%), beneficial effects in terms of symptom reduction are unquestioned. Due to the single arm design, the effect on PFS and OS cannot be properly evaluated but a detrimental effect is considered unlikely. Combination therapy is highly likely to provide symptomatic benefit.

Overall, combination treatment is associated with a high incidence of ADRs, including grade 3 events. However, the safety and tolerability of the combination treatment is considered acceptable and manageable.

3.6.2. Balance of benefits and risks

The combination of dabrafenib and trametinib has demonstrated high antitumor activity that is clinically relevant. The safety and tolerability of the combination treatment is considered acceptable and manageable. The CHMP considers that the benefit – risk balance of the combination therapy in the treatment of NSCLC harbouring the BRAF V600 mutation is favourable.

3.7. Conclusions

The overall B/R of the combination of dabrafenib and trametinib for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation is positive.

4. Recommendations

Outcome

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

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

Extension of indication to include the combination treatment with trametinib and dabrafenib of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the Mekinist SmPC and sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the Tafinlar SmPC are updated. The Package Leaflet and RMP (version 13.1 for Mekinist and 8.3 for Tafinlar) are updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to bring the Product Information for both products in line with the latest QRD template version 10.

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

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include the combination treatment with trametinib and dabrafenib of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the Mekinist SmPC and sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the Tafinlar SmPC are updated. The Package Leaflet and RMP (version 13.1 for Mekinist and 8.3 for Tafinlar) are updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to bring the Product Information for both products in line with the latest QRD template version 10.

Summary

Please refer to the published assessment report Mekinist-Tafinlar-WS-0996: EPAR - Assessment Report – Variation