2 September 2015
EMA/589140/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mekinist	Trametinib
Tafinlar	Dabrafenib

Procedure No. EMEA/H/C/WS/0736

Note

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

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1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Glaxo Group Limited submitted to the European Medicines Agency on 7 April 2015 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

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

Extension of indication to add a new therapeutic indication for the use in combination of trametinib and dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly. An updated RMP was also provided.

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

These Marketing Authorisations have now been transferred to Novartis Europharm Ltd on 20 April 2015 for Mekinist and on 6 May 2015 for Tafinlar.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included the EMA Decisions P/0078/2014 (Mekinist) and P/0332/2014 (Tafinlar) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0078/2014 (Mekinist) and P/0332/2014 (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.

Applicant's request(s) for consideration

Additional data protection / marketing exclusivity

The applicant requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The applicant received Scientific Advice from the CHMP on 14 April 2011.

1.2. Steps taken for the assessment of the product

Appointed (Co-)Rapporteurs for the WS procedure:

Pieter de Graeff

Filip Josephson

Timetable	Actual dates
Submission date	7 April 2015
Start of procedure:	25 April 2015
CHMP Co-Rapporteur Assessment Report	3 July 2015
PRAC Rapporteur Assessment Report	3 July 2015
CHMP Rapporteur Assessment Report	23 June 2015
PRAC Outcome	9 July 2015
Updated CHMP Rapporteur Assessment Report	15 July 2015
Updated PRAC Rapporteur Assessment Report	17 July 2015
Opinion	23 July 2015
The CHMP adopted an Assessment Report on the novelty of the significant clinical benefit in comparison with existing therapies (see Appendix 1)	23 July 2015

2. Scientific discussion

2.1. Introduction

RAF, MEK1 and MEK2 are proteins in the RAS/RAF/MEK/ERK pathway (i.e., the mitogen-activated protein kinase [MAPK] pathway) which is a critical proliferation pathway involved in normal cellular functions as well as in many human cancers, relating to regulation of cell proliferation. The pathway affects many cancers, in particular melanoma where BRAF mutations are present in 50% of melanoma[1]. The most frequently observed BRAF mutation in melanoma was shown to be V600 (74-90%)[2] . Oncogenic mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway.

[1] Davies H, et al. Mutations of the BRAF gene in human cancer. Nature; 417:949-954, 2002
[2] Garnett MJ and Marais R. Guilty as charged: B-RAF is a human oncogene. Cancer Cell 6:313-319, 2004

There are currently two small molecule inhibitors of BRAFV600 (Zelboraf and Tafinlar) and one small molecule inhibitor of MEK (Mekinist) that have been approved. Both trametinib and dabrafenib are currently approved as monotherapy for the treatment of adult patients with unresectable or metastatic melanoma that expresses a somatic gene mutation known as BRAF V600 mutation. Mekinist (trametinib) was granted a marketing authorisation on June 30th 2014, and Tafinlar (dabrafenib) on August 26th 2013.

The pivotal registration study for dabrafenib was the phase III BRF113683 study in which the efficacy and safety of dabrafenib was compared with DTIC. In this study, a statistically significant improvement in PFS (HR 0.37; 95% CI 0.24, 0.58; p<0.0001) was seen where median PFS for dabrafenib was 6.9 months compared to 2.7 months with DTIC. The median OS for dabrafenib was 20.0 months in comparison to 15.6 months for DTIC (HR 0.77; 95% CI 0.52, 1.13).

In the pivotal phase III study of trametinib MEK114267, the median PFS was 4.8 for patients treated with trametinib and 1.5 months for patients treated with chemotherapy (HR 0.45; 95% CI 0.33, 0.63; p<0.0001). The median OS was 15.6 and 11.3 months for patients in the trametinib and chemotherapy arms respectively (HR 0.78; 95%CI 0.57,1.06).

The clinical benefit of monotherapy with BRAF and MEK inhibitors appears to be limited by the development of resistance, with approximately 50% of the patients treated with BRAF inhibitors progress within 5 to 7 months after starting treatment. There are several mechanisms of acquired resistance to BRAF and MEK inhibitors that have been proposed. However, the main pathway for resistance is thought to be the reactivation of the MAPK pathway through alternative activation of downstream MEK. Thus, trametinib and dabrafenib combination would inhibit two kinases in this pathway, MEK and RAF, and provide concomitant inhibition of the pathway. It is suggested that inhibiting both MEK and BRAF simultaneously could postpone or possibly prevent the development of resistance.

Other treatment options have been approved for melanoma in recent times, namely treatments that target the immune system instead of targeting the cancer itself. In 2011, the anti-CTLA4 antibody ipilimumab (Yervoy) was approved for the treatment of advanced (unresectable or metastatic) melanoma in adults. More recently, additional immunotherapeutic options available include the monoclonal antibodies nivolumab (Opdivo) and pembrolizumab (Keytruda) for the treatment of advanced (unresectable or metastatic) melanoma in adults.

The applicant has applied for an extension of the indication for both trametinib and dabrafenib MAs to include the combination of trametinib with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

The applicant applied for the following indications:

"Dabrafenib in combination with trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation."

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

The final approved indications are as follows:

Mekinist

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

Trametinib monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy (see section 5.1)."

Tafinlar

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

The recommended dose of trametinib, either used as monotherapy or in combination with dabrafenib, is 2 mg once daily (QD). The recommended dose of dabrafenib, when used in combination with trametinib, is 150 mg twice daily (BID) (see SmPC section 4.2).

The recommended dose of dabrafenib, either used as monotherapy or in combination with trametinib, is 150 mg (two 75 mg capsules) twice daily (corresponding to a total daily dose of 300 mg). The recommended dose of trametinib, when used in combination with dabrafenib, is 2 mg once daily (QD) (see SmPC section 4.2).

Patients should take trametinib as monotherapy or in combination with dabrafenib at least one hour prior to or two hours after a meal due to the effect of food on trametinib absorption (see section 4.2 and 5.2).

2.2. Non-clinical aspects

2.2.1. Introduction

Trametinib and dabrafenib as single agents have shown growth inhibition of BRAF V600 mutant melanoma cell lines and demonstrate anti-tumour effects in BRAF V600 mutant melanoma animal models. The non-clinical aspects of the combination of trametinib and dabrafenib have been presented in the initial marketing authorisation application. In summary, the data submitted had shown that the combination resulted *in vitro* cell growth inhibition in cells that harboured human BRAFV600 mutations and for those that had become resistant to dabrafenib treatment. *In vivo* in A375PF11 BRAFV600E human melanoma mouse xenografts, the combination treatment showed a delayed tumour resistance and significant survival improvement with prolonged tumour growth inhibition and delayed tumour outgrowth when compared to treatment with the single agents individually. Sequential administration of one week dabrafenib (30 mg/kg) and the other week trametinib (3 mg/kg) for 11 weeks showed prolonged tumour growth inhibition.

A repeat dose toxicity study in dogs receiving trametinib (0.0075/5 or 0.0225/20 mg/kg/day for trametinib/dabrafenib) resulted in decreased food consumption, abnormal faeces, decrease in body weight which resulted in mortality in one male rat. Microscopic findings were observed in the heart, colon, rectum, mesenteric lymph nodes and thymus. There was evidence of toxicity to the heart and coronary arteries and veins, with vascular changes characterized by endothelial hypertrophy, intimal proliferation, disruption of the internal elastic lamina and fibrinoid necrosis of the tunica media, and perivascular inflammation leading to haemorrhage.

Proliferative skin lesions such as epithelial hyperplasia/hyperkeratosis of the skin and forestomach mucosa induced with dabrafenib treatment alone administered for at least 2 weeks were not observed in the combination study.

Toxicity was observed in the male and female reproductive organs. Testicular toxicity characterised by testicular degeneration and secondary epididymal oligospermia was observed in rats and dogs in a 13 week toxicity study. After 4 week recovery period, there was no sign of reversibility. In females, toxicity characterised by alteration in follicular maturation was observed in a repeat toxicity study. The effects were reversible following 4 weeks recovery period. Developmental toxicities were observed in rats given dabrafenib, and in rats and rabbits given trametinib. These effects occurred at exposures below those in patients receiving recommended doses and were considered to be related to pharmacology.

2.2.2. Pharmacology

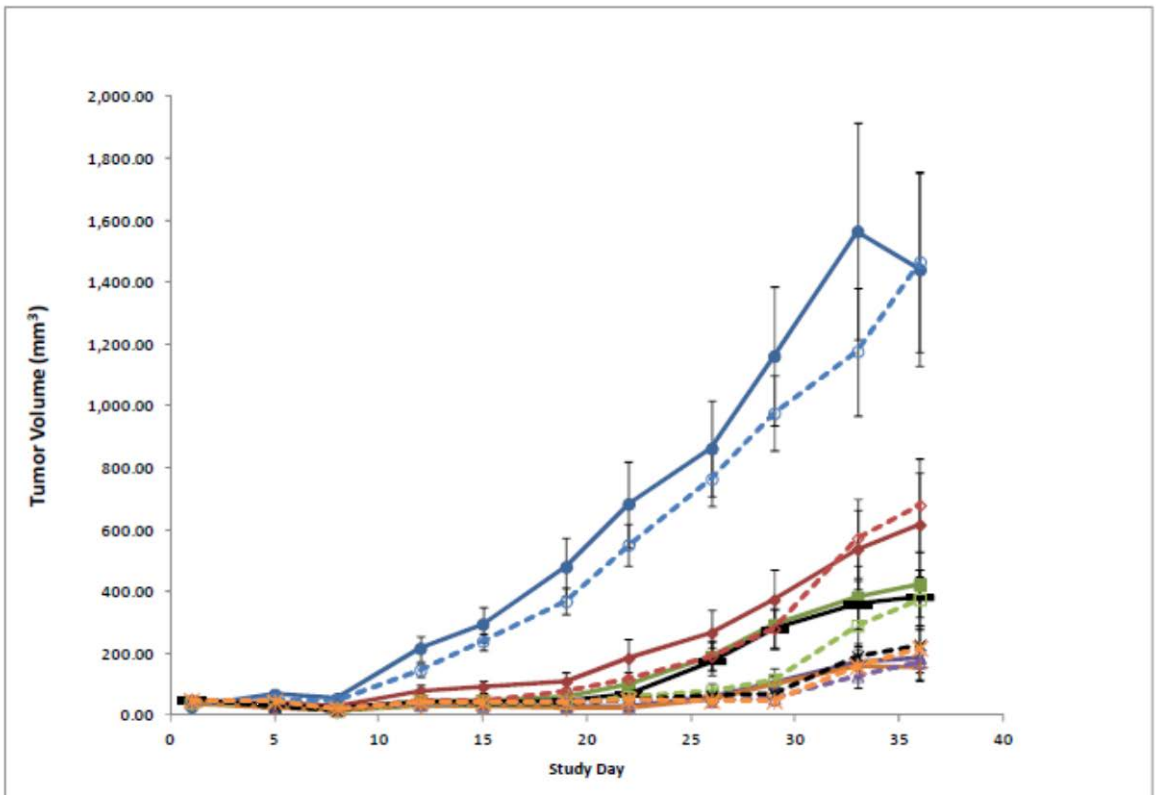
Two additional primary pharmacodynamics studies have been performed. These *in vivo* studies examined the effect of combination dosing in a mouse BRAF mutant human melanoma xenograft model.

Primary pharmacodynamic studies

Anti-tumour effect of dabrafenib and trametinib in melanoma xenografted mice (study 2012N152372)

Female CD-1 nude mice were xenografted with the A375P F11 cell line, encoding a mutation for $BRAF^{V600E}$. The xenografted mice (n=15/group) were administered trametinib (0.3 or 1 mg/kg/day), dabrafenib (30 mg/kg/day) or a combination thereof orally by gavage for 14 or 28 days.

Figure 1: Effect of dabrafenib alone or in combination with trametinib on A375P F11s tumour growth in nude mice

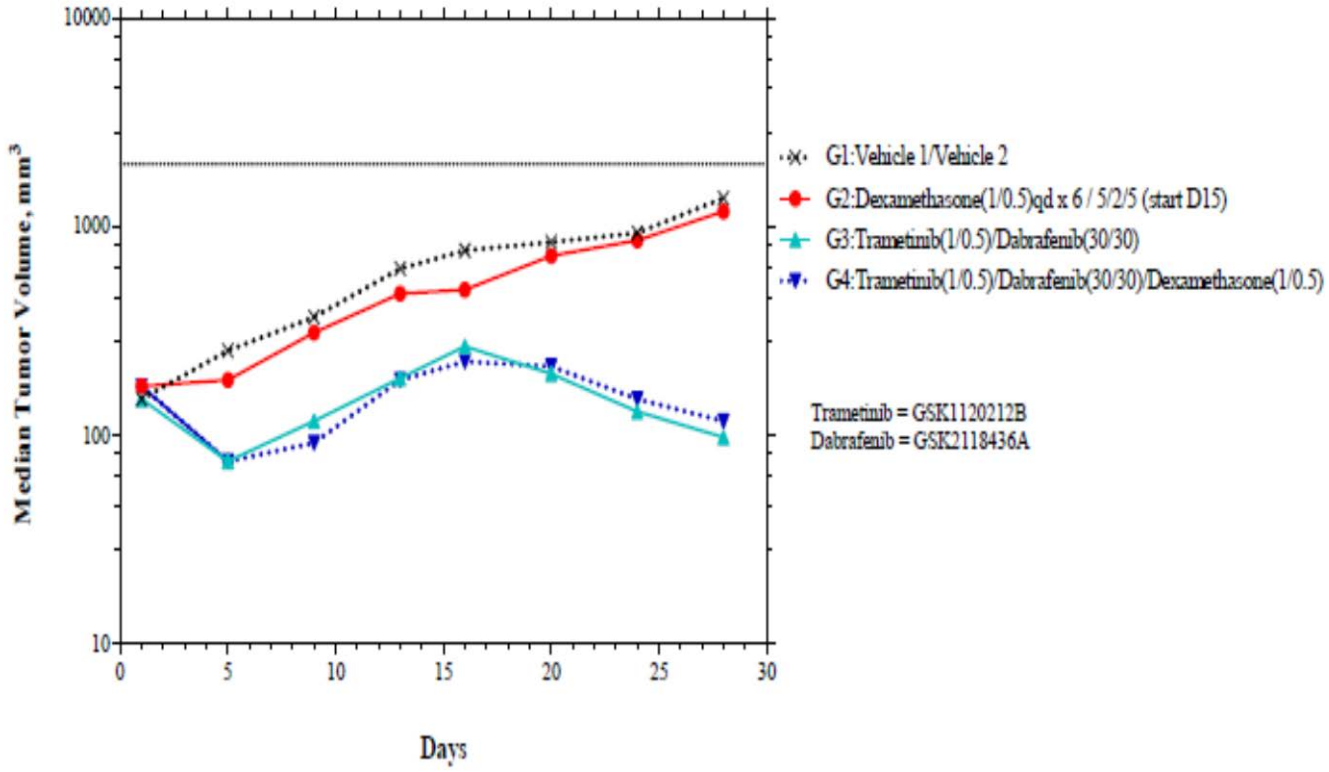


Bold line = 14 day exposure; dashed line = 28 day exposure. Blue = vehicle control; red = dabrafenib 30 mg/kg; green = trametinib 0.3 mg/kg; purple = trametinib 1 mg/kg; black = 0.3 mg/kg trametinib + dabrafenib 30 mg/kg; orange = trametinib 1 mg/kg + dabrafenib 30 mg/kg.

Anti-tumour effect of dabrafenib and trametinib with dexamethasone in melanoma xenografted mice (study 2014n201242)

Female athymic nude mice were xenografted with the A375P F11 cell line, encoding a mutation for $BRAF^{V600E}$. Mice were treated with 1 mg/kg/day trametinib and 30 mg/kg/day dabrafenib with or without 1 mg/kg/day dexamethasone for 28 days. Treatment was interrupted due to overt toxicity at day 6 and continued at day 15 through day 28. From day 15, mice were treated with 0.5 mg/kg/day trametinib, 30 mg/kg/day dabrafenib and 0.5 mg/kg dexamethasone on a five days on/two days off schedule. The anti-tumour efficacy of the trametinib and dabrafenib combination was not affected by addition of dexamethasone.

Figure 2: Median tumour growth in A375P F11s in athymic mice following treatment trametinib, dabrafenib and dexamethasone



Addition of dexamethasone also induced a body weight loss of more than 20%. Due to the weight loss observed with triple combination therapy, a dosing holiday was given for all groups on Day 6. Body weights recovered, and dosing resumed on D15 with trametinib and dabrafenib.

2.2.3. Ecotoxicity / environmental risk assessment

Table 1: Summary of main study results

<table>
<tr><td colspan="6">Substance (INN / Invented Name): dabrafenib / Tafinlar</td></tr>
<tr><td colspan="6">CAS-number (if available): 1195768-06-9</td></tr>
<tr><td>PBT screening</td><td></td><td colspan="2">Result</td><td colspan="2">Conclusion</td></tr>
<tr><td>Bioaccumulation potential- log K_{ow}</td><td>OECD107</td><td colspan="2">Log Dow (pH 7) = 3.384</td><td colspan="2">Potential PBT (Y/N)</td></tr>
<tr><td colspan="6">PBT-assessment</td></tr>
<tr><td>Parameter</td><td>Result relevant for conclusion</td><td colspan="2"></td><td colspan="2">Conclusion</td></tr>
<tr><td rowspan="2">Bioaccumulation</td><td>log K_{ow}</td><td colspan="2">3.384</td><td colspan="2">not B</td></tr>
<tr><td>BCF</td><td colspan="2"><10</td><td colspan="2"></td></tr>
<tr><td>Persistence</td><td>DT50 or ready biodegradability</td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>Toxicity</td><td>NOEC or CMR</td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>PBT-statement :</td><td colspan="5">The compound is not considered as PBT nor vPvB</td></tr>
<tr><td colspan="6">Phase I</td></tr>
<tr><td>Calculation</td><td>Value</td><td colspan="2">Unit</td><td colspan="2">Conclusion</td></tr>
<tr><td>PEC $_{surfacewater}$</td><td>1.5 (default)
0.36 (refined based on prevalence)</td><td colspan="2">µg/L</td><td colspan="2">> 0.01 threshold</td></tr>
<tr><td>Other concerns (e.g. chemical class)</td><td></td><td colspan="2"></td><td colspan="2">No</td></tr>
<tr><td colspan="6">Phase II Physical-chemical properties and fate</td></tr>
<tr><td>Study type</td><td>Test protocol</td><td colspan="2">Results</td><td colspan="2">Remarks</td></tr>
<tr><td>Adsorption-Desorption</td><td>OECD 106</td><td colspan="2"><table><tr><td></td><td colspan="2">Adsorption</td><td colspan="2">Desorption</td></tr><tr><td></td><td>Kd</td><td>Koc</td><td>Kd</td><td>Koc</td></tr><tr><td>Soil A</td><td>157.1</td><td>5,819</td><td>223</td><td>8,258</td></tr><tr><td>Soil B</td><td>84.9</td><td>10,615</td><td>132.1</td><td>16,516</td></tr><tr><td>Soil C</td><td>54.9</td><td>1445</td><td>67.1</td><td>1765</td></tr><tr><td>Sediment</td><td>121.9</td><td>2,345</td><td>132.8</td><td>2,553</td></tr></table></td><td colspan="2"></td></tr>
<tr><td>Adsorption-Desorption</td><td>OPPTs 835.1110</td><td colspan="2">K_{oc} =2460</td><td colspan="2"></td></tr>
<tr><td>Ready Biodegradability Test</td><td>OECD 301</td><td colspan="2">Not inherently biodegradable
Ultimate biodegradation (DOC) = 0%
Primary degradation = 81%</td><td colspan="2"></td></tr>
<tr><td>Aerobic and Anaerobic Transformation in Aquatic Sediment systems</td><td>OECD 308</td><td colspan="2">$DT_{50,\ whole\ system}$ =162-307 days</td><td colspan="2"></td></tr>
<tr><td colspan="6">Phase IIa Effect studies</td></tr>
<tr><td>Study type</td><td>Test protocol</td><td>Endpoint</td><td>value</td><td>Unit</td><td>Remarks</td></tr>
<tr><td>Algae, Growth Inhibition Test/ Pseudokirchneriella subcapitata</td><td>OECD 201</td><td>NOEC</td><td>0.22</td><td>mg/ L</td><td></td></tr>
<tr><td>Daphnia sp. Reproduction Test</td><td>OECD 211</td><td>NOEC</td><td>0.105</td><td>mg/ L</td><td>No toxicity observed but upper limit of test limited by low water solubility</td></tr>
<tr><td>Fish, Early Life Stage Toxicity Test/ Pimephales promelas</td><td>OECD 210</td><td>NOEC</td><td>1.47</td><td>mg/ L</td><td></td></tr>
<tr><td>Activated Sludge, Respiration Inhibition Test</td><td>OECD 209</td><td>NOEC</td><td>312.5</td><td>mg/ L</td><td></td></tr>
<tr><td colspan="6">Phase IIb Studies</td></tr>
<tr><td>Bioaccumulation</td><td>OECD 305</td><td colspan="3">0.01 mg/L
BCFss = 4.38
BCFk = 3.46</td><td>Oncorhynchus mykiss</td></tr>
</table>

		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			
Sediment dwelling organism, water chironomid toxicity test	OECD 218	NOEC	64	mg/ kg	*Chironomus riparius*

2.2.4. Discussion on non-clinical aspects

The non-clinical data for the combination treatment of dabrafenib and trametinib was previously presented and assessed as part of the monotherapy application for trametinib. In order to support the combination therapy, the MAH submitted two new pharmacology studies that showed that the combination of trametinib and dabrafenib inhibited the growth of tumours in *in vivo* models. Exposure to the combination of dabrafenib and trametinib in xenograft V600 mutant mice models showed an increase in tumour response as compared to the monotherapy of either dabrafenib or trametinib alone. The tumour response observed was not influenced by the use of the anti-inflammatory and immunosuppressant corticosteroid dexamethasone. Therefore, the combination of trametinib with dabrafenib showed anti-tumour activity in BRAF V600 mutation positive melanoma cell lines *in vitro* and delays the emergence of resistance *in vivo* in BRAF V600 mutation positive melanoma xenografts.

There were no new toxicity findings in the studies submitted compared to the non-clinical data presented in the trametinib and dabrafenib initial marketing authorisation applications. Toxicity studies in dogs have shown some increase in toxicity compared to monotherapy where trametinib and dabrafenib were given in combination for 4 weeks, signs of gastro-intestinal toxicity and decreased lymphoid cellularity of the thymus were observed at lower exposures than in dogs given trametinib alone. Otherwise, similar toxicities were observed as in comparable monotherapy studies.

Development toxicity was observed in the monotherapy for dabrafenib and trametinib. The findings suggest a risk for human embryofoetal development, including teratogenic effects. It is reasonable to presume that the effect of the combination treatment on developmental toxicity would not differ from the monotherapy. This has already been addressed previously in the trametinib and dabrafenib initial applications, where development toxicity was identified as an important potential risk or as missing information and will be monitored as an important potential risk through routine risk minimisation measures.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of trametinib in combination with dabrafenib. Considering the above data, trametinib in combination with dabrafenib is not expected to pose a risk to the environment.

2.2.5. Conclusion on the non-clinical aspects

The non-clinical studies were considered adequate and acceptable for the assessment of non-clinical aspects of an application for the extension of indication for the combination therapy of trametinib with dabrafenib.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 2: Overview of studies evaluating the efficacy of combination dabrafenib and trametinib in unresectable or metastatic BRAF V600 mutation-positive melanoma

Study	Phase III Study MEK115306	Phase III Study MEK116513	Phase II Study BRF113220 Part C
Critical design features	Randomized, double-blinded, 2-arm	Randomized, open-label, 2-arm	Randomized, open-label, 3-arm; crossover to 150/2 combination allowed after progression on monotherapy
Number of subjects randomized (ITT): Study treatment	N=423 • Combination therapy: n=211 • Dabrafenib monotherapy (dabrafenib + trametinib placebo): n=212	N=704 • Combination therapy: n=352 • Vemurafenib: n=352	N=162[a] • Dabrafenib monotherapy: n=54 • 150/1 combination: n=54[a] • 150/2 combination: n=54
Primary efficacy endpoint(s)	PFS	OS	PFS, ORR (CR+PR), Duration of Response
Secondary efficacy endpoint(s) and [exploratory endpoints]	OS, ORR (CR+PR), Duration of response, [HRQOL]	PFS, ORR (CR+PR), Duration of response, [HRQOL]	OS
Primary Data cut-off	26 August 2013	17 April 2014[b]	31 May 2012
Updated analysis cut-off	12 Jan 2015	NA	15 Jan 2014
Module location	m5.3.5.1	m5.3.5.1	m5.3.5.1

a This overview presents results of the 150/2 combination therapy arm and the dabrafenib monotherapy arm. Results of the 150/1 combination therapy arm are available in the BRF113220 Part C Primary CSR and Final OS aCSR.

b At the interim analysis, Study MEK116513 met the primary objective (OS). The Independent Data Monitoring Committee met on 09 July 2014 and recommended stopping the study for efficacy. As such, the interim OS summary is considered the final comparative OS analysis.

2.3.2. Pharmacokinetics

The clinical pharmacology characteristics of dabrafenib and trametinib when administered as monotherapy and in combination have been described previously in the monotherapy applications for trametinib[3] and dabrafenib[4] .

[3] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002643/WC500169708.pdf
[4] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002604/WC500149673.pdf

PK data for the combination were obtained from the Phase I/II, open-label, dose-escalation Study BRF113220, and the pivotal Phase III, randomized, double-blinded Study MEK115306. In part A, the effect of repeat doses of trametinib 2 mg once daily on single dose dabrafenib was investigated, part B was a dose escalation and cohort expansion of combination dabrafenib and trametinib, Part C was a randomized Phase II part of the study including dabrafenib 150 mg BID as monotherapy and in combination with trametinib 1 and 2 mg once daily, and in Part D, PK and safety of dabrafenib 75 and 150 mg BID administered as hydroxypropyl methylcellulose or hypromellose (HPMC) capsules as monotherapy and in combination with trametinib 2 mg once daily was assessed.

Study BRF113220 Part A: interaction between trametinib and dabrafenib

Trametinib had shown inhibitory potential against CYP2C8 *in vitro*, with a concentration resulting in 50% of maximum inhibition (IC50) of 0.34 µM. *In vitro* studies demonstrated that the oxidative metabolism of dabrafenib was mediated by CYP2C8 and could potentially be affected by CYP2C8 inhibitors.

A total of 8 subjects were included in Part A. GLS means ratios of dabrafenib plus trametinib to dabrafenib alone (90% CI) were 1.03 (0.79, 1.34), 1.01 (0.85, 1.19), and 0.94 (0.82, 1.08) for Cmax, AUC(0-t) and AUCinf, respectively. The 90% CI for AUCs were contained within the 80 to 125% boundaries. Median tmax was 2.5 and 2.0 hours with administration of dabrafenib alone and with trametinib, respectively. Similar results were noted with dabrafenib metabolites including hydroxy-,carboxy- and desmethyl-dabrafenib with GLS mean dabrafenib plus trametinib to dabrafenib alone ratios ranging from 0.92 to 1.03 for the different PK parameters.

Study BRF113220 Part B: dose escalation and cohort expansion of combination dabrafenib and trametinib

The initial dose of the combination was half the recommended dose of each agent. Doses of trametinib 1, 1.5, and 2 mg once-daily were administered in combination with dabrafenib (75 or 150 mg BID, gelatin capsules) using a dose escalation procedure. The dose proportionality of trametinib was evaluated using a power model.

Dose escalation proceeded until the recommended single agent doses of dabrafenib (150 mg BID) and trametinib (2 mg once daily). One subject experienced a dose limiting toxicity of neutrophilic panniculitis in Part B, at a dose of dabrafenib 150 mg BID and trametinib 2 mg once daily. A total of 79 subjects were treated.

Dabrafenib: The geometric mean AUCinf following administration of dabrafenib 150 mg BID (gelatin capsule) in combination with trametinib 1, 1.5, or 2 mg trametinib ranged from 3539 to 5187 ng*hr/mL on Day 15 (n=13) and from 4528 to 5518 ng*hr/mL on Day 21 (n=28).

Trametinib: At doses of 1, 1.5, and 2 mg once-daily, geometric mean trametinib AUC(0-8), AUCinf, Cmax and C_τ on Days 15 (n = 20) and 21 (n = 35) increased in a dose-proportional manner. Following administration of trametinib 2 mg once-daily doses, geometric mean (% between subject coefficient of variability [CVb]) Cmax, AUCinf and C_τ were 22.4 ng/mL (30%), 394 ng*hr/mL (35%), and 12.4 ng/mL (42%), respectively, on Day 15 and 22.6 ng/mL (36%), 351 ng*hr/mL (34%), and 10.8 ng/mL (34%), respectively, on Day 21.

Study BRF113220 Part D: PK and safety of dabrafenib 75 and 150 mg BID administered as HPMC capsules as monotherapy and in combination with trametinib 2 mg once daily

Dabrafenib: PK parameters for dabrafenib after dosing 75 and 150 mg BID with/without trametinib 2 mg once daily are provided in Table 3.

Table 3: Summary of dabrafenib plasma PK parameters following single and repeat-dosing of dabrafenib 75 mg and 150 mg twice daily (HPMC Capsules)

administered alone and in combination with trametinib - Study BRF113220 Part D

	Dosing Regimen (Dabrafenib + Trametinib)			
Dabrafenib Dose	**75 mg BID**	**75 mg BID**	**150 mg BID**	**150 mg BID**
Trametinib Dose	**-**	**2.0 mg daily**	**-**	**2.0 mg daily**
Day 1 PK				
n	15	15	14 [d]	15
Tmax (hr)	2.00 (1.00-3.00)	2.00 (1.00-3.00)	2.00 (1.00-6.00)	1.50 (1.00-10.0)
Cmax (ng/mL)	1117 (37.5)	1277 (63.7)	1669 (92.7)	2289 (68.8)
AUC(0-τ) (ng*hr/mL)	3593 (33.0)	4618 (51.8)	6507 (78.1)[b]	7331 (61.6)
AUC(0-∞) (ng*hr/mL)	3982 (32.0)[b]	5321 (41.1)[c]	7291 (76.9)[b]	8152 (62.2)[b]
t1/2 (hr)	3.8 (23.3)[b]	3.9 (21.0)[c]	4.1 (19.9)[b]	3.6 (36.4)[b]
Day 21 PK				
n	14 [d]	14 [d]	11 [e]	12 [f]
Tmax (hr)	1.50 (1.00-2.00)	1.75 (1.00-3.00)	1.55 (0.98-3.00)	1.50 (1.00-3.00)
Cmax (ng/mL)	1050 (47.0)	1217 (57.2)	1746 (40.5)	2052 (56.0)
AUC(0-τ) (ng*hr/mL)[a]	3020 (42.2)	3434 (45.1)	4663 (44.2)	5886 (40.0)
Cτ (ng/mL)	28.0 (175)	63.3 (149)	77.4 (215)	72.1 (106)
Day21:Day1 Ratios				
AUC(0-τ) Ratio	0.85 (38.6)	0.71 (34.6)	0.65 (79.5) [b]	0.73 (42.7)

Trametinib: PK parameters for trametinib 2 mg once daily with dabrafenib 75 and 150 mg BID are provided in Table 4.

Table 4: Summary of trametinib plasma PK parameters following single and repeat-dosing of trametinib 2 mg once daily in combination with dabrafenib 75 and 150 mg twice daily - Study BRF113220 Part D

	Dosing Regimen (Dabrafenib + Trametinib)	
Dabrafenib Dose	**75 mg BID**	**150 mg BID**
Trametinib Dose	**2 mg daily**	**2 mg daily**
Day 1 PK		
n	15	14
Tmax (hr)	2.00 (1.00-3.00)	1.50 (1.00-8.00)
Cmax (ng/mL)	6.8 (74.9)	6.6 (85.7)
AUC(0-τ) (ng*hr/mL)	53.4 (57.8)	50.7 (46.8)
Day 21 PK		
n	14	13
Tmax (hr)	2.00 (1.00-4.00)	2.00 (1.50-3.98)
Cmax (ng/mL)	24.1 (30.2)	22.6 (24.8)
AUC(0-τ) (ng*hr/mL)[a]	366 (32.3)	356 (19.3)
Cτ (ng/mL)	11.2 (34.3)	10.9 (22.6)
Day21:Day1		
AUC(0-τ) Ratio	6.5 (34.4)	7.2 (42.8)

Trametinib and dabrafenib PK parameters obtained in combination were generally consistent throughout studies BRF113220, BRF113683 and BRF 113771.

The final validated models developed for the combination were used to evaluate data obtained in the Phase III study MEK115306 and provide post hoc estimates. Individual post hoc estimates for CL/F and Vc/F are listed in Table 5.

Table 5: Geometric mean (%CV) individual post-hoc pharmacokinetic parameter estimates for dabrafenib - Study 2013N184875_00

Pharmacokinetic Parameter	Dabrafenib Monotherapy (N=191)	Dabrafenib + Trametinib (N=201)
CL/F (L/hr)	38.9 (30.0%)	35.9 (33.6%)
Vc/F (L)	68.2 (40.5%)	78.5 (38.3%)

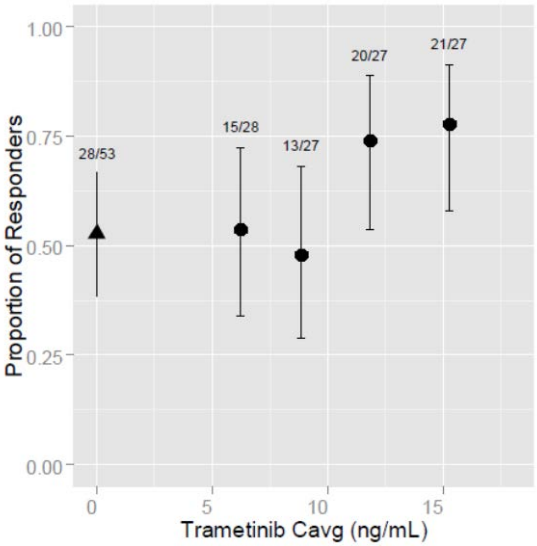
2.3.3. Pharmacodynamics

Pop-PK: exposure-response

Response Rate (Study BRF113220, Part C)

The relationship between response rate and exposure was explored graphically by binning data into quartiles of exposure (Study 2012N144949_02). Figure 3 shows an increase in response rate with higher trametinib average exposure (≥10 ng/mL). These data support selection of combination dose with trametinib 2 mg once daily.

Figure 3: Proportion of responders as a function of trametinib exposure from subjects enrolled - Study BRF113220 Part C



There was no relationship between response rate and dabrafenib or dabrafenib metabolites exposure across dabrafenib monotherapy and combination cohorts.

Progression-Free Survival (Study MEK115306)

The relationship between PFS and quartiles of exposure was explored based on results from the Phase III study MEK115306 (Study 2013N184875_00). Results are shown in Figure 4 and Figure 5 for dabrafenib and trametinib, respectively.

Figure 4: Progression-Free Survival curves by quartiles of dabrafenib exposure (Cavg) in subjects receiving dabrafenib monotherapy (Left) and in combination with trametinib (Right) - Study MEK115306

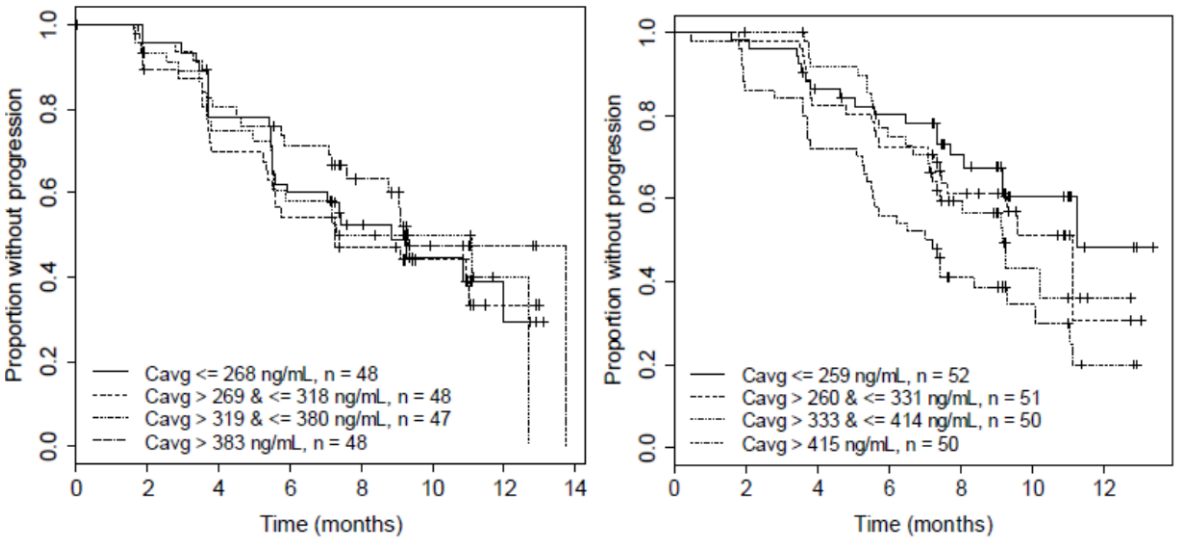
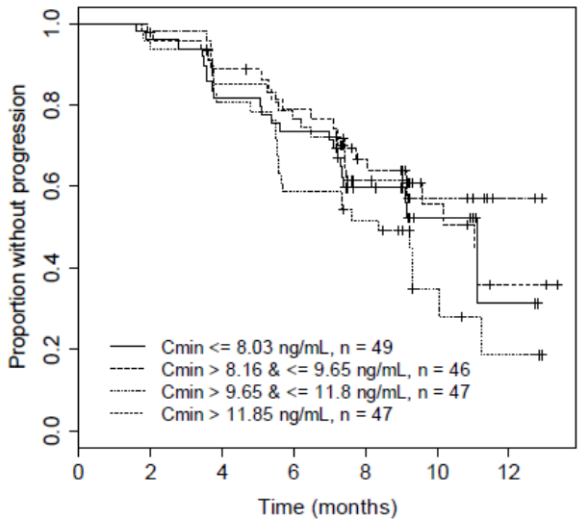


Figure 5: Progression-Free Survival curves by quartiles of trametinib exposure (Cmin) in subjects receiving dabrafenib and trametinib in combination - Study MEK115306



Adverse Events

The relationship between pyrexia and exposure was explored by plotting the safety data against quartiles of exposure in Study MEK115306 (Study 2013N184875_00) or tertiles of exposure in Study BRF113220 Part C (Study 2012N144949_02). The analysis was performed on pyrexia events.

Higher rates of pyrexia were noted when dabrafenib was administered with trametinib (Figure 6). The incidence of pyrexia tended to be higher with higher trametinib exposure when administered in combination.

Figure 6: Incidence of pyrexia by quartiles of exposure to dabrafenib (Top) and hydroxy-dabrafenib (Bottom) in subjects receiving dabrafenib monotherapy (Left, Study BRF113220 Part C) and in combination with trametinib (Right, Study MEK115306)

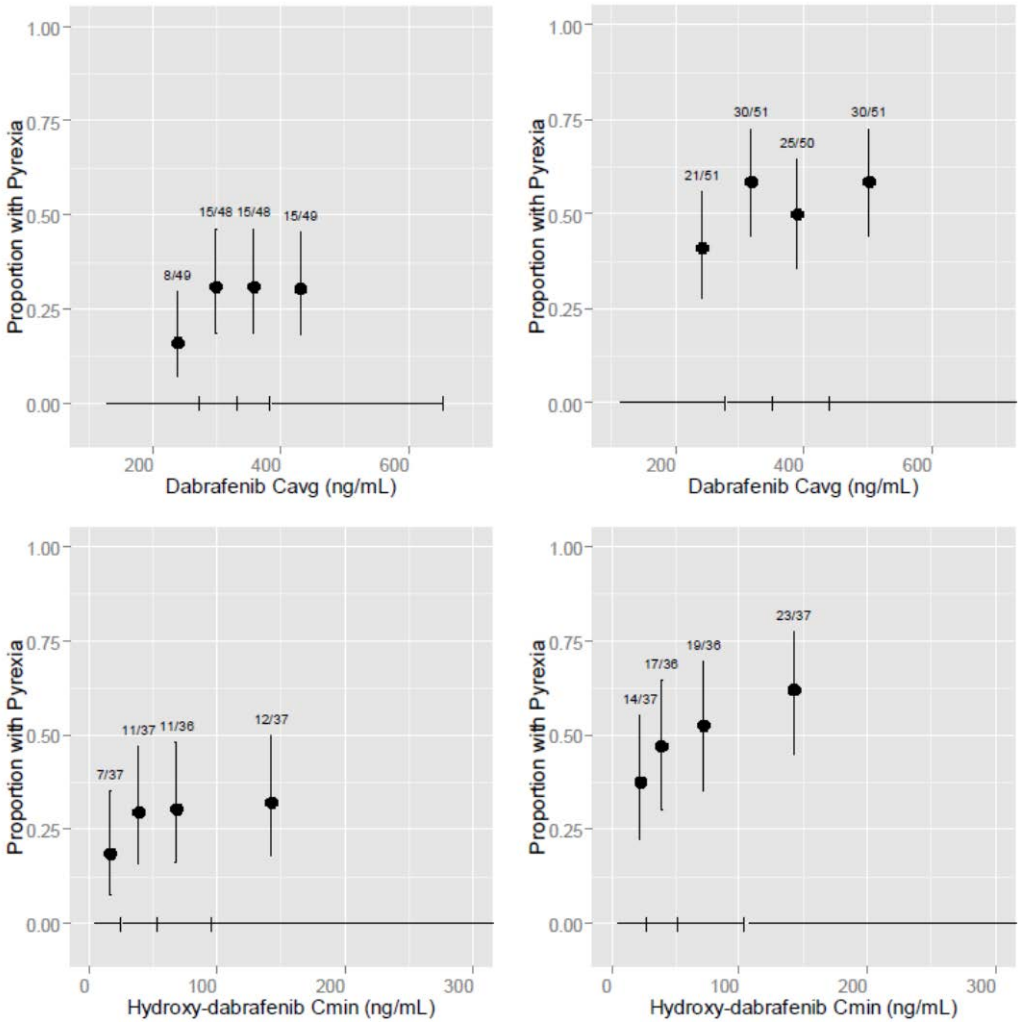
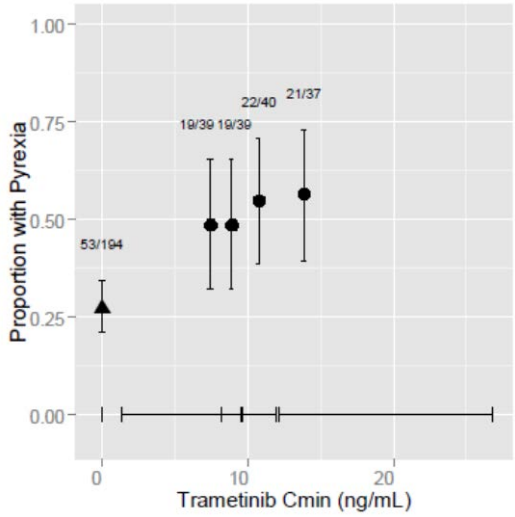


Figure 7: Incidence of pyrexia by quartiles of exposure to trametinib in subjects receiving dabrafenib and trametinib in combination - Study MEK115306



2.3.4. Discussion on clinical pharmacology

The clinical pharmacology characteristics of dabrafenib and trametinib when administered as monotherapy, as well as the clinical pharmacology characteristics of dabrafenib and trametinib administered in combination have been well characterized and have been described previously in the monotherapy applications (EMEA/H/C/2604 and EMEA/H/C/2643).

When given in combination, the recommended dose of the combination is 150 mg twice-daily (BID) of dabrafenib with 2 mg once-daily of trametinib, administered under fasting conditions. These doses in combination are equal to the doses applied for the individual drugs dabrafenib and trametinib when given as monotherapy.

Based on the data obtained from Study BFR113220, co-administration of repeat dosing of trametinib and dabrafenib resulted in no clinically meaningful changes in trametinib or dabrafenib C_{max} and AUC with increases of 16 and 23 %, respectively. A small decrease in trametinib bioavailability, corresponding to a decrease in AUC of 12 %, was estimated when trametinib is administered in combination with dabrafenib, a CYP3A4 inducer, using a population PK analysis. Therefore, administration of dabrafenib and trametinib in combination had no clinically relevant effect on the exposure of trametinib or of dabrafenib relative to administration of either compound alone.

With dabrafenib and trametinib given in combination at a 150 mg BID and 2 mg OD dose, there was no apparent relationship between PFS and dabrafenib or trametinib exposure but there was a noted increase in responses with higher exposure to trametinib.

When trametinib is used in combination with dabrafenib, concurrent administration of strong inhibitors or strong inducers of CYP3A4 or CYP2C8 should be avoided (see section 4.4 and 4.5 of dabrafenib and trametinib SmPC).

An increase in the proportion of subjects experiencing pyrexia was noted with administration of trametinib in combination with dabrafenib, compared to administration of dabrafenib as monotherapy. Incidence of pyrexia tended to be higher with higher trametinib exposure when administered in combination. Although rate of pyrexia was not related to dabrafenib concentrations, a trend toward higher rates of pyrexia was noted with higher hydroxy-dabrafenib concentrations upon combining dabrafenib 150 mg and trametinib

2 mg. Pyrexia is a known important identified risk with dabrafenib which is already addressed in the RMP and monitored through routine minimisation measures.

2.3.5. Conclusions on clinical pharmacology

The data provided is considered sufficient to characterise the PK and PD of an application for the extension of indication for the combination therapy of trametinib with dabrafenib.

2.4. Clinical efficacy

The clinical efficacy for the combination of trametinib and dabrafenib treatment in unresectable and metastatic melanoma patients in melanoma patients with tumours harbouring BRAFV600 mutation was supported by the submission of an update to the phase II study BRF113220 and by the two phase III studies, MEK115306 which evaluated the treatment of dabrafenib in combination trametinib vs dabrafenib in untreated melanoma patients and study MEK116513, which evaluated the treatment of dabrafenib in combination trametinib vs vemurafenib in untreated melanoma patients with BRAFV600 tumours. Headline results for study MEK115306 have been evaluated in the initial marketing authorisation for trametinib.

2.4.1. Dose response study

2.4.2. Dose response study BRF113220 on the combination of dabrafenib and trametinib

Study BRF113220 was performed to determine the optimal dosage of trametinib when applied 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. The endpoints for ORR, PFS and DoR are presented in Table 6, 7, and 8, respectively.

Table 6: Investigator-assessed best confirmed response (%), RECIST 1.1, part B melanoma subjects, BRAFi-naïve - Study BRF113220

	B-1 (N=6)	B-2 (N=22)	B-3 (N=25)	B-4 (N=24)	Total (N=77)
Best Response					
Complete response	0	4 (18)	0	2 (8)	6 (8)
Partial response	4 (67)	10 (45)	11 (44)	13 (54)	38 (49)
Stable disease	2 (33)	7 (32)	11 (44)	9 (38)	29 (38)
Non-CR/Non-PD	0	0	1 (4)	0	1 (1)
Progressive disease	0	1 (5)	2 (8)	0	3 (4)
Response Rate					
CR+PR	4 (67)	14 (64)	11 (44)	15 (63)	44 (57)
95% Confidence Interval [a]	(22.3%,95.7)	(40.7%,82.8)	(24.4%,65.1)	(40.6%,81.2)	(45.4%,68.4)

Data Source; Table 12.79

Abbreviations: B-1=dabrafenib 75 mg BID + trametinib 1 mg daily; B-2=dabrafenib 150 mg BID + trametinib 1 mg daily; B-3=dabrafenib 150 mg BID + trametinib 1.5 mg daily; B-4=dabrafenib 150 mg BID + trametinib 2 mg daily.

a. Confidence interval calculated using the exact method.

Table 7: Investigator-assessed progression-free survival, part B melanoma subjects, BRAFi naïve - Study BRF113220

	B-1 (N=6)	B-2 (N=22)	B-3 (N=25)	B-4 (N=24)	Total (N=77)
Number of Subjects					
n	6	22	25	24	77
Progressed or Died (event)	5 (83)	17 (77)	20 (80)	17 (71)	59 (77)
Censored, Follow-up ended	0	0	0	1 (4)	1 (1)
Censored, Follow-up ongoing	1 (17)	5 (23)	5 (20)	6 (25)	17 (22)
Estimates for Progression-free Survival (Months)					
1st Quartile (95%CI) [a]	5.3 (3.4,11.8)	4.3 (3.5,7.3)	3.3 (2.9,4.5)	3.6 (3.5,9.1)	3.6 (3.5,5.3)
Median (95%CI) [a]	8.7 (5.3,16.6)	8.2 (5.4,11.0)	5.4 (3.5,12.8)	10.8 (5.3,14.4)	7.4 (5.5,11.0)
3rd Quartile (95%CI) [a]	16.6 (5.6,.)	14.8 (9.2,.)	12.9 (5.5,.)	18.6 (11.3,18.6)	14.8 (11.8,.)

Data Source: Table 12.83

Abbreviations: BB-1=dabrafenib 75 mg BID + trametinib 1 mg daily; B-2=dabrafenib 150 mg BID + trametinib 1 mg daily; B-3=dabrafenib 150 mg BID + trametinib 1.5 mg daily; B-4=dabrafenib 150 mg BID + trametinib 2 mg daily.

a. Confidence Intervals estimated using the Brookmeyer Crowley method. Time to event start date is defined as the date of first dose

Table 8: Investigator-assessed duration of response, part B melanoma subjects, BRAFi naïve - Study BRF113220

	B-1 (N=6)	B-2 (N=22)	B-3 (N=25)	B-4 (N=24)	Total (N=77)
Number of Subjects with a Confirmed Response					
n	4	14	11	15	44
Progressed or Died (event)	3 (75)	9 (64)	6 (55)	8 (53)	26 (59)
Censored, Follow-up ended	0	0	0	1 (7)	1 (2)
Censored, Follow-up ongoing	1 (25)	5 (36)	5 (45)	6 (40)	17 (39)
Duration of Response (Months)					
1st Quartile (95% CI) [a]	6.9 (3.7,14.9)	5.5 (3.6,9.2)	6.5 (3.7,12.6)	9.1 (3.7,16.9)	6.5 (3.9,10.0)
Median (95% CI) [a]	12.4 (3.7,14.9)	8.4 (5.5,.)	12.6 (6.5,.)	11.3 (9.1,16.9)	11.3 (9.2,16.9)
3rd Quartile (95% CI) [a]	14.9 (10.0,14.9)	. (7.6,.)	. (11.1,.)	16.9 (11.3,16.9)	. (14.9,.)

Data Source: Table 12.90

Abbreviations: B-1=dabrafenib 75 mg BID + trametinib 1 mg daily; B-2=dabrafenib 150 mg BID + trametinib 1 mg daily; B-3=dabrafenib 150 mg BID + trametinib 1.5 mg daily; B-4=dabrafenib 150 mg BID + trametinib 2 mg daily.

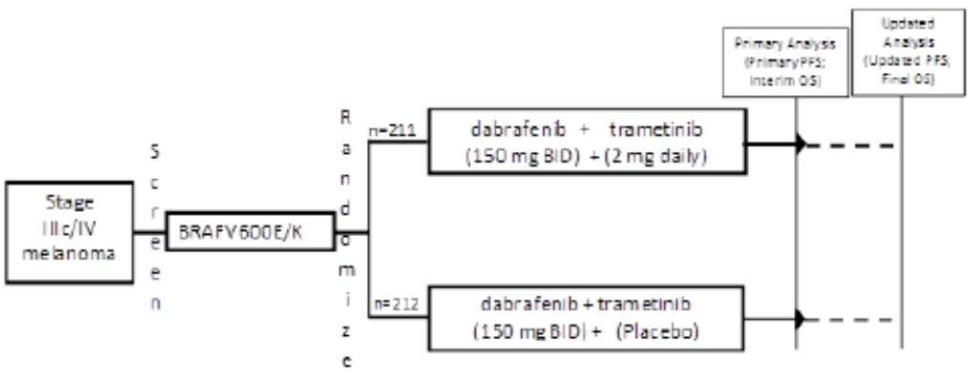
a. Confidence interval calculated from the Kaplan-Meier estimates.

2.4.3. Main studies

MEK115306: A Phase III, randomized, double-blinded study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo as first-line therapy in subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma

Methods

The full assessment of the design and conduct of this study was assessed as the time of the initial marketing authorisation application. The MEK115306 study schema is presented below.



Study participants

- Key inclusion criteria included the following:
- ≥18 years of age

- Histologically confirmed cutaneous melanoma that is either Stage IIIC (unresectable) or Stage IV (metastatic), and determined to be BRAF V600E/K mutation-positive using the bioMerieux Investigational Use Only (IUO) THxID BRAF Assay (Investigational Device Exemption [IDE]: G120011). The assay will be conducted by a central reference laboratory. Subjects with ocular or mucosal melanoma are not eligible
- Measurable disease (i.e., present with at least 1 measurable lesion per RECIST, version 1.1).
- All prior anti-cancer treatment-related toxicities (except alopecia and laboratory values) must be ≤Grade 1 according to the Common Terminology Criteria for Adverse Events, version 4 (CTCAE version 4.0; [NCI, 2009]) at the time of randomization.
- Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to randomization and agree to use effective contraception throughout the treatment period, and for 4 months after the last dose of study treatment.

Key exclusion criteria included the following:

- Prior treatment with a BRAF inhibitor (including but not limited to dabrafenib, vemurafenib, LGX818, and XL281/BMS-908662) or a MEK inhibitor (including but not limited to trametinib, AZD6244, and RDEA119).
- Prior systemic anti-cancer treatment (chemotherapy, immunotherapy, biologic therapy, vaccine therapy, or investigational treatment) for Stage IIIC (unresectable) or Stage IV (metastatic) melanoma. Prior systemic treatment in the adjuvant setting is allowed. (Note: Ipilimumab treatment must end at least 8 weeks prior to randomization.)
- Any major surgery, extensive radiotherapy, chemotherapy with delayed toxicity, biologic therapy, or immunotherapy within 21 days prior to randomization, or daily or weekly chemotherapy without the potential for delayed toxicity within 14 days prior to randomization.
- Taken an investigational drug within 28 days or 5 half-lives (minimum 14 days), whichever is shorter, prior to randomization.
- History of another malignancy.
    - Exception: Subjects who have been disease-free for 3 years, or subjects with a history of completely resected non-melanoma skin cancer, or subjects with indolent second malignancies are eligible.
- A history of glucose-6-phosphate dehydrogenase deficiency.
- Brain metastasis are excluded unless:
    - All known lesions have been definitively treated with surgery or stereotactic surgery (whole-brain radiation may be given as adjuvant treatment) , OR
    - Brain lesion(s), if still present, must be confirmed stable (i.e., no increase in lesion size) for ≥ 12 weeks prior to randomization (stability must be confirmed with 2 consecutive magnetic resonance imaging (MRI) or computed tomography (CT) scans with contrast separated by ≥ 6 weeks), AND
    - Asymptomatic with no corticosteroid requirements for ≥ 4 weeks prior to randomization, AND
    - No enzyme inducing anticonvulsants for ≥ 4 weeks prior to randomization

- In addition, for subjects that had brain metastases but currently had no evidence of disease (NED), NED for ≥ 12 weeks was required and must have been confirmed by 2 consecutive scans, separated by ≥ 6 weeks, prior to randomization.

- A history or evidence of cardiovascular risk including any of the following:
- A QT interval corrected for heart rate using the Bazett's formula (QTcB; see protocol, Appendix 3) ≥480 msec;
- A history or evidence of current clinically significant uncontrolled arrhythmias;
  - Exception: Subjects with atrial fibrillation controlled for > 30 days prior to randomization are eligible.
  - A history (within 6 months prior to randomization) of acute coronary syndromes (including myocardial infarction or unstable angina), coronary angioplasty;
  - A history or evidence of current Class II congestive heart failure as defined by the New York Heart Association guidelines (see protocol, Appendix 4);
  - Treatment refractory hypertension defined as a blood pressure of systolic> 140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by antihypertensive therapy;
  - Subjects with intra-cardiac defibrillators or permanent pacemakers;
  - Known cardiac metastases;
  - Abnormal cardiac valve morphology (≥ Grade 2) documented by echocardiogram (subjects with Grade 1 abnormalities [i.e., mild regurgitation/stenosis] can be entered on study). Subjects with moderate valvular thickening should not be entered on study.
- A history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR) including:
  - Presence of predisposing factors to RVO or CSR (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled hypertension, uncontrolled diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes)
  - Visible retinal pathology as assessed by ophthalmic examination that is considered a risk factor for RVO or CSR such as:
    - Evidence of new optic disc cupping;
    - Evidence of new visual field defects on automated perimetry;
    - Intraocular pressure >21 mmHg as measured by tonography.

Treatments

Dabrafenib and trametinib were administered orally at the recommended doses of 150 mg twice daily and 2 mg once daily, respectively. Subjects in the combination therapy arm received both active agents, while subjects in the dabrafenib monotherapy arm received dabrafenib at the recommended dose of 150 mg twice daily with a placebo.

Patients were to be treated until disease progression, unacceptable toxicity or patient refusal. Up to 2 dose reductions due to toxicity were allowed. Of note, after protocol amendments 1, 4 and 6, patients experiencing disease progression were allowed to continue treatment beyond progression at discretion of investigator if they had achieved an objective (partial or complete) response. Cross-over from the

dabrafenib + placebo arm to the combination arm was not allowed.

Objectives

Primary:

To establish the superiority of dabrafenib and trametinib combination therapy over dabrafenib and placebo (dabrafenib monotherapy) with respect to progression-free survival (PFS) for subjects with advanced/metastatic BRAF V600E/K mutation-positive cutaneous melanoma.

Secondary:

The secondary objectives of this study were:

- To compare dabrafenib and trametinib combination therapy with dabrafenib monotherapy for overall survival (OS) (key secondary), overall response rate (ORR), and duration of response
- To characterize the safety of dabrafenib and trametinib combination therapy, including incidences of squamous cell carcinoma (SCC) and other proliferative cutaneous lesions; and
- To characterize the concentrations of trametinib and of dabrafenib and its metabolites in subjects in the combination arm and of dabrafenib and its metabolites in the dabrafenib monotherapy arm

Outcomes / endpoints

The primary endpoint was Progression-Free Survival (PFS) defined as the time from randomisation until the earliest date of disease progression or death due to any cause.

Secondary endpoints were as follows:

- Overall survival (OS) as defined as the time from randomization until death due to any cause.
- Overall response rate was defined as the percentage of subjects with a confirmed complete response [CR] or partial response [PR] at any time per Response Evaluation Criteria in Solid Tumours [RECIST], version 1.1.
- Duration of response was defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause among subjects who achieve an overall response.
- Safety as measured by clinical assessments including vital signs and physical examinations, 12-lead electrocardiograms (ECG), echocardiogram (ECHO), chemistry and haematology laboratory values, incidence of squamous cell carcinoma, and adverse events (AEs).
- Concentrations of trametinib and of dabrafenib and its metabolites (GSK2285403, GSK2298683, and GSK2167542) in the combination arm and dabrafenib and its metabolites in the dabrafenib monotherapy arm.

Exploratory endpoints were as follows:

- Changes from baseline in HRQOL measures assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) and the EuroQol-5D (EQ-5D).
- Apparent clearance following oral dosing (CL/F), volume of distribution (V/F), and the effect of combination therapy on CL/F, exposure-response with tumour size, and other clinical/safety measures, as warranted.

- Tumour DNA, RNA, and protein content, other tumour tissue aberrations, clinical outcome, and tumor response.
- BRAF mutations in cfDNA, tumour tissue mutations, other mutations in circulating cfDNA and tumour response.
- Genetic variants, safety measures (as listed under secondary endpoints), frequency of dose modifications and/ or interruptions, and tumour response.

Sample size

The study was designed to have 90% power to detect a 70% increase in PFS (i.e., HR: 0.5889, median PFS of 5.3 and 9 months in the dabrafenib monotherapy arm and the combination therapy arm, respectively). Assuming one-sided overall alpha of 0.025, power of 90%, and a randomization ratio of 1:1 a total of 155 events (progression or deaths) were estimated to be required. According to the statistical plan (SAP), with 155 events it would have been possible to detect an improvement as low as 37.7% (HR=0.726 which equates to median PFS of 7.3 and 5.3 months, respectively) with statistical significance. At the time of the final PFS analysis an interim OS was planned. According to the SAP, patients were to be followed for survival until 70% of the total enrolled population died or lost to follow-up. Given a projected recruitment of 18 subjects per month over the first 6 months, and 75 subjects per month thereafter resulting in enrolment duration of approximately 9 months, 340 patients were originally planned.

According to the Applicant due to 24% over-enrolment (423 patients instead of the planned 340), it was decided to perform the final PFS analysis after 193 events (instead of the originally planned 155) which represents the same percentage (45.6%) of total enrolment as originally planned. This change was expected to increase the overall power from 90% to 95%.

Randomisation

A total of 423 patients were randomized (1:1) to receive either dabrafenib 150 mg BID plus trametinib 2 mg QD or dabrafenib 150 mg BID plus placebo dabrafenib. Randomisation was stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) versus ≤ ULN) and BRAF mutation (V600E vs V600K).

Blinding (masking)

The study was designed as a double-blinded study.

Statistical methods

Time to event-endpoints were analysed using Kaplan-Meier methods, the stratified log-rank test and the Pike estimator for the hazard ratio and its confidence interval were used. A stepwise Cox regression explored for PFS the influence of 1. Prior immunotherapy (Yes vs. No), 2. Baseline ECOG performance status (0 vs. 1), 3. Stage at Screening (III, IVM1a, IVM1b vs. IVM1c), 4. Visceral Disease at Baseline (yes vs. no), 5. Number of disease sites at baseline (<3 vs. ≥3), 6. Gender (Male vs. Female), and 7. Age (continuous).

Primary endpoint: PFS

- Censoring rules were as follows:

Situation	Date of Progression or Censoring	Outcome
No baseline (or post baseline adequate) tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Date of assessment of progression[1]	Progressed
No progression (or death)	Date of last 'adequate' assessment of response[2]	Censored
New anti-cancer treatment started prior to documented disease progression.[3]	Date of last 'adequate' assessment of response[2] on or prior to starting anti-cancer therapy	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than two or more missed visits	Date of last 'adequate' assessment of response[2] prior to missed assessments	Censored

[1] The earliest of (i) Date of radiological assessment showing new lesion; or (ii) Date of radiological assessment showing unequivocal progression in non target lesions, or (iii) Date of last radiological assessment of target lesions (if progression is based on increase in sum of measured lesions).

[2] An adequate assessment is defined as an assessment where the ivestigator determined response is CR, PR, or SD.

[3] If PD and New anti-cancer therapy occur on the same day assume the progression was documented first. e.g. outcome is progression and the date is the date of the assessment of progression). If anti-cancer therapy is started prior to any adequate assessments, censoring date should be the date of randomization.

- Sensitivity analyses included: symptomatic progression as events, considering start of new anti-cancer therapy as an event, considering radiological progression after extended loss to follow-up or start of new anti-cancer therapy as an event, and stratified Cox regression analysis.
- Over-enrolment was expected to induce more censorings and therefore bias in the estimation of the median in the combination arm if the original timing (155 events out of 340 patients, so at 45.6% of total sample size) was kept. Therefore the timing was changed proportionally to 45.6% of 423, so 193 events.

Key secondary endpoints: OS.

- An interim analysis using a Lan alpha-spending function, with O'Brien like boundaries was performed.

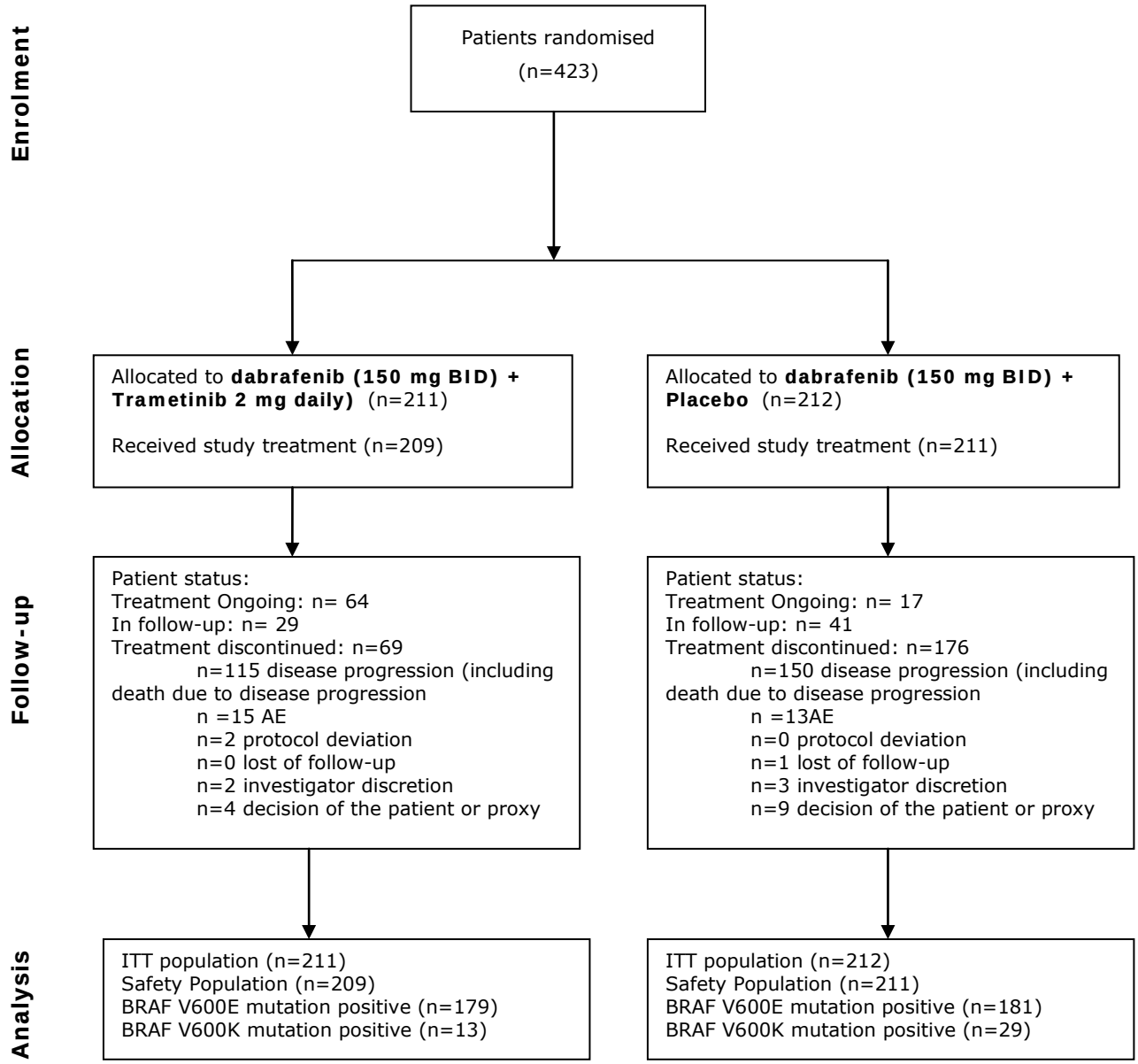
ORR was per investigator and were tabulated based on the number and percentage of subjects attaining an overall confirmed CR or PR in subjects with measurable disease at baseline. Subjects with non-evaluable best response were imputed as non-responders.

QLQ-C30 and EQ5D were analyzed using a mixed model for repeated measurements.

Multiplicity: OS was tested hierarchically after PFS.

Results

Participant flow



Recruitment

A total of 423 patients were enrolled at 103 centres in 14 countries, including Germany (25 centres), the US (12 centres), and the UK (10 centres) as well as Argentina, Australia, Canada, Spain, France, Greece, Italy, Netherlands, Russian Federation, Sweden and Ukraine). Patients were included from February 2012 and the data cut-off for this study was 12 January 2015.

Conduct of the study

An external independent Data Monitoring Committee (DMC) monitored the conduct of the study, periodically assessed safety information, and also reviewed efficacy data of the interim analyses. The original MEK115306 Protocol, date 08 February 2012, was amended 8 times. The latest amendment was at 12 August 2014. The purpose of this amendment was to increase the time to study closure to obtain longer-term survival data; provide drug-specific instruction in cases where a dose is missed; update list of concomitant medications; modify and/or clary dose modification guidelines for LVEF, hypertension, QTc prolongation, hand-food skin reactions, cuSCC, pyrexia, renal insufficiency, visual changes, and pneumonitis; add guidelines for new primary melanoma, non-cutaneous malignancies, pancreatitis, hyperglycaemia, and retinal pigment epithelia detachment; remove blood sample collection for cytokine analysis during a pyrexic event; clarify treatment of study treatment overdose regarding haemodialysis; add a descriptive analysis of PFS, DoR and ORR at the final analysis; add final OS analysis, based on US FDA feedback, to be performed at 220 events rather than 275 and descriptive OS update at 275 events; add text to allow eligible patients to crossover to combination therapy if a statistically significant and clinically meaningful OS benefit is observed at the final OS analysis.

Baseline data

Table 9: Demographic characteristics - Study MEK115306

		Dabrafenib + Trametinib (N=211)	Dabrafenib + Placebo (N=212)	Total (n=423)
Age (yrs)	N	211	212	423
	Mean	55.1	55.3	55.2
	SD	13.33	13.75	13.52
	Median	55.0	56.5	56.0
	Min.	22	22	22
	Max.	89	86	89
Age group (yrs)	<18	0	0	0
	18-64	154 (73)	151 (71)	305 (72)
	65-74	45 (21)	43 (20)	88 (21)
	75-84	10 (5)	17 (8)	27 (6)
	>=85	2 (<1)	1 (<1)	3 (<1)
Sex	N	211	212	423
	Female	100 (47)	98 (46)	198 (47)
	Male	111 (53)	114 (54)	225 (53)

Table 10: Baseline disease characteristics - Study MEK115306

	Dabrafenib + Trametinib (N=211)	Dabrafenib + Placebo (N=212)	Total (n=423)
Measurable disease at baseline			
Yes	210 (>99)	210 (>99)	420 (>99)
No	0	1 (<1)	1 (<1)
Stage at screening			
IIIc	5 (2)	10 (5)	15 (4)
IV	206 (98)	201 (95)	407 (96)
M1a	19 (9)	31 (15)	50 (12)
M1b	45 (21)	32 (15)	77 (18)
M1c	142 (67)	138 (65)	280 (66)
Visceral disease at baseline			
Yes	165 (78)	145 (68)	310 (73)
No	46 (22)	66 (31)	112 (26)
Number of disease sites at baseline			
< 3 sites	109 (52)	119 (56)	228 (54)
>=3 sites	101 (48)	92 (43)	193 (46)
Prior immunotherapy			
Yes	56 (27)	61 (29)	117 (28)
No	155 (73)	151 (71)	306 (72)
ECOG PS at baseline			
1	54 (26)	61 (29)	115 (27)
0	155 (73)	150 (71)	305 (72)

Table 11: Stratification factors - Study MEK115306

	Dabrafenib + Trametinib (N=211)	Dabrafenib + Placebo (N=212)	Total (n=423)
Baseline LDH			
Above ULN	76 (36)	76 (36)	152 (36)
Equal to or below ULN	135 (64)	136 (64)	271 (64)
BRAF mutation status			
V600E	178 (84)	179 (84)	357 (84)
V600K	33 (16)	33 (16)	66 (16)

Numbers analysed

All 423 randomized subjects were included in the ITT population.

Table 12: Study population - Study MEK115306

Population	Dabrafenib + Trametinib (N=211)	Dabrafenib + Placebo (N=212)	Total (N=423)
Intent-to-treat[a]	211	212	423
Safety[b]	209	211	420
Braf V600E mutation positive[c]	179	181	360
Braf V600K mutation positive[c]	32	29	61

Data Source: Table 1.0010

Note: Details for the pharmacokinetics study population are presented in the MEK115306 Primary CSR, Section 5.3.

a. All randomized subjects are included in the Intent-to-Treat population regardless of whether or not they received study treatment.

b. Subjects are included in the Safety population if they have been randomized and taken at least 1 dose of study treatment.

c. BRAF V600E and BRAF V600K mutation-positive populations are subsets of the ITT population. In the

Outcomes and estimation

At the time of the data cut-off (12 January 2015), 44% of subjects in the dabrafenib and trametinib (combination therapy) arm and 36% of subjects in the dabrafenib monotherapy arm were still ongoing in the study.

Primary endpoint: Progression-Free Survival

The following analysis for PFS was conducted with a data lock point of 26 August 2013.

Table 13: PFS by Investigator and BIRC Assessment - Study MEK115306

	Investigator Assessment		BIRC Assessment	
	Dabrafenib+ Trametinib (N=211)	Dabrafenib+ Placebo (N=212)	Dabrafenib+ Trametinib (N=211)	Dabrafenib+ Placebo (N=212)
Number of subjects				
Progressed or died (event)	102 (48)	109 (51)	93 (44)	94 (44)
Censored, follow-up ended	14 (7)	22 (10)	24 (11)	40 (19)
Censored, follow-up ongoing	95 (45)	81 (38)	94 (45)	78 (37)
Estimates for progression-free survival(months)				
1st quartile	5.6	3.7	5.7	4.6
95% CI	(4.8, 6.5)	(3.6, 5.3)	(5.3, 7.1)	(3.7, 5.5)
Median	9.3	8.8	10.1	9.5
95% CI	(7.7, 11.1)	(5.9, 10.9)	(8.3, 11.8)	(7.3, 12.7)
3rd quartile		13.7	13.2	13.9
95% CI	(11.2,)	(12.0, 13.7)	(11.8, 13.2)	(12.7, 13.9)
Adjusted hazard ratio				
Estimate	0.75		0.78	
95% CI	(0.57, 0.99)		(0.59, 1.04)	
Stratified log-rank p-value	0.035		0.085	

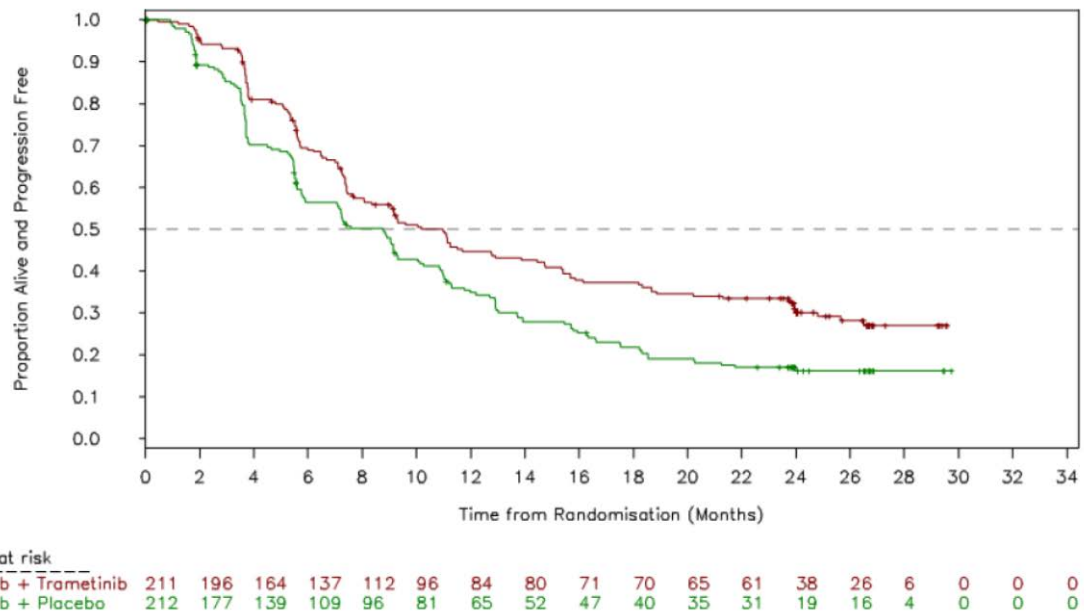
An updated analysis for PFS by investigator assessment was based on events in 66% and 76% of the patients, respectively in the combination therapy and monotherapy arms. Median PFS for the combination therapy arm was 11.0 months compared with 8.8 months for the dabrafenib monotherapy arm with HR 0.67 (95% CI: 0.53, 0.84; p<0.001).

Table 14: Summary of investigator-assessed progression-free survival (ITT population) - Study MEK115306 (data cut-off date of 12 January 2015)

	Dabrafenib + Trametinib (N=211)	Dabrafenib + Placebo (N=212)
Number of Subjects, n (%)		
Progressed or Died (event)	139 (66)	162 (76)
Censored, follow-up ended	17 (8)	20 (9)
Censored, follow-up ongoing	55 (26)	30 (14)
Estimates for Progression-Free Survival (months)[a]		
1st Quartile (95% CI)	5.5 (4.8, 6.2)	3.7 (3.5, 5.0)
Median (95% CI)	11.0 (8.0, 13.9)	8.8 (5.9, 9.3)
3rd Quartile (95% CI)	NR (24.0, NR)	16.3 (12.9, 18.5)
Adjusted Hazard Ratio[b]		
Estimate (95% CI)	0.67 (0.53, 0.84)	
Stratified Log-Rank P-Value[b]	<0.001	

a. Quartiles estimated using the Brookmeyer - Crowley method [Brookmeyer R, 1982].
b. Hazard ratios are estimated using a Pike estimator. A hazard ratio <1 indicates a lower risk with dabrafenib + trametinib compared with dabrafenib + placebo. Hazard ratio and p-value from stratified log-rank test are adjusted for randomized strata: baseline LDH and BRAF mutation status.

Figure 8: Investigator-assessed Kaplan-Meier PFS curves (ITT population) - Study MEK115306 (data cut-off date of 12 January 2015)



A total of 62 (29%) patients in the combination therapy arm and 65 (31%) patients in the dabrafenib monotherapy arm continued to receive study treatment for at least 15 days after disease progression. At the time of the data cut off, 13/62 and 6/65 patients remained on combination therapy and dabrafenib monotherapy, respectively.

Secondary Endpoints

Overall Survival

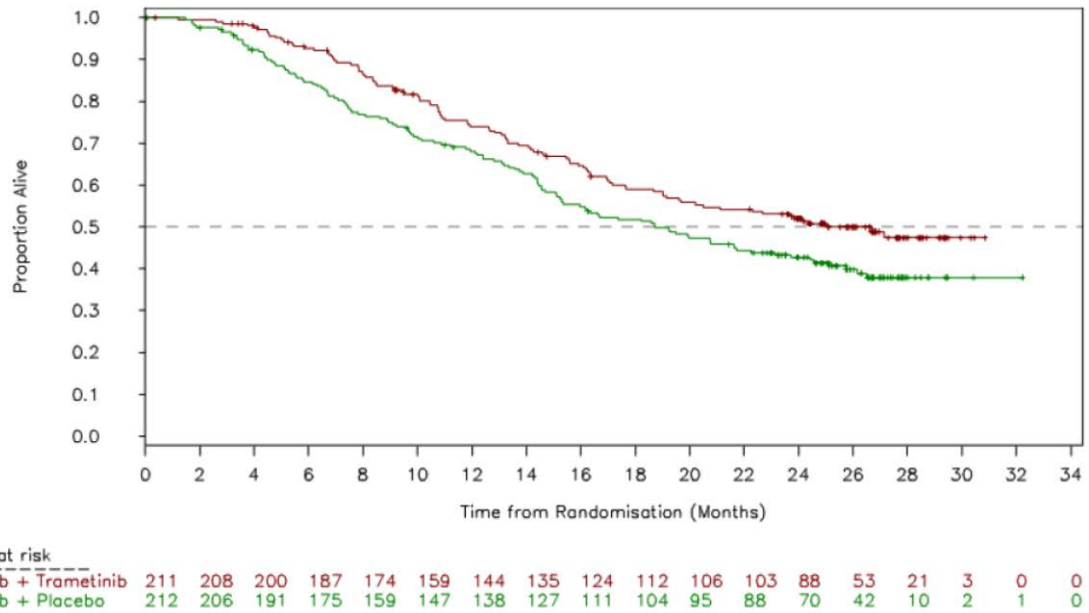
With the final OS analysis a statistically significant reduction in risk of death for the combination therapy arm compared with the dabrafenib monotherapy arm was reported (HR 0.71, 95% CI: 0.55, 0.92; p=0.011). The median OS was 25.1 months for the combination therapy arm and 18.7 months for the dabrafenib monotherapy arm.

Table 15: Summary of overall survival (ITT population) - Study MEK115306 (data cut-off date of 12 January 2015)

	Dabrafenib + Trametinib (N=211)	Dabrafenib + Placebo (N=212)
Number of Subjects, n (%)		
Died (event)[a]	99 (47)	123 (58)
Censored, follow-up ended	19 (9)	13 (6)
Censored, follow-up ongoing	93 (44)	76 (36)
Estimates for Overall Survival (months)[b]		
1st Quartile (95% CI)	11.9 (10.1, 14.2)	8.9 (7.1, 11.8)
Median (95% CI)	25.1 (19.2, NR)	18.7 (15.2, 23.7)
3rd Quartile (95% CI)	NR (NR, NR)	NR (NR, NR)
Adjusted Hazard Ratio[b]		
Estimate (95% CI)	0.71 (0.55, 0.92)	
Stratified Log-Rank P-Value [c]	0.011	
Estimates for Overall Survival at 1 and 2 Years		
1 year (95% CI)	73.5% (66.8, 79.0)	67.6% (60.8, 73.5)
2 years (95% CI)	51.4% (44.1, 58.2)	42.1% (35.2, 48.8)

a. Includes 4 subjects who withdrew but subsequently had date of death recorded.
b. Quartiles estimated using the Brookmeyer - Crowley method [Brookmeyer R, 1982].
c. Hazard ratios are estimated using a Pike estimator. A hazard ratio <1 indicates a lower risk with dabrafenib + trametinib compared with dabrafenib + placebo. Hazard ratio and p-value from stratified log-rank test are adjusted for randomized strata: baseline LDH and BRAF mutation status.

Figure 9: Kaplan-Meier estimates on overall survival (ITT population) - Study MEK115306 (data cut-off date of 12 January 2015)



Overall Response Rate

Investigator-assessed ORR results at the time of the final OS analysis showed a statistically significant difference in the combination therapy arm compared with the dabrafenib monotherapy arm (15% difference, 95% CI: 6.0, 24.5; p=0.0014).

Table 16: Response rate by investigator assessment (subjects with measurable disease at baseline by RECIST v1.1 criteria) (ITT population) - Study MEK115306 (data cut-off date of 12 January 2015)

	Dabrafenib + trametinib (n=210)	Dabrafenib + placebo (n=210)
Best response		
Complete response	33 (16)	28 (13)
Partial response	111 (53)	84 (40)
Stable disease	50 (24)	66 (31)
Progressive disease	13 (6)	19 (9)
Not evaluable	3 (1)	13 (6)
Response rate		
CR+PR	144 (69)	112 (53)
95% confidence interval	(61.8, 74.8)	(46.3, 60.2)
Difference in response rate		
CR+PR	15%[b]	
95% confidence interval for difference	(6.0, 24.5)	
P-value[a]	0.0014	

a. Chi-squared test was used to calculate the p-value.
b. Note that the difference in response rates was calculated prior to rounding the response rates to whole numbers.

Ancillary analyses

Analysis including Symptomatic Progressions: PFS is analyzed the same as the primary endpoint with the addition that symptomatic progressions are also considered as events.

Considering start of new anti-cancer therapy as an event: PFS is analyzed the same as the primary endpoint with the addition that the start of new anticancer therapy is considered as an event, even if radiological progression was not documented.

Analysis ignoring extended loss to follow up and start of new anti-cancer therapy: Progression (based only on radiologic evidence) or death is considered an event regardless of whether it occurred after extended lost to follow-up or initiation of a new anti-cancer therapy. If a subject has neither progressed nor died, then PFS is censored at the date of the last 'adequate' assessment.

Table 17: PFS sensitivity analyses - Study MEK115306 (data cut-off: 26 August 2013)

	Include Symptomatic PD as an Event		Include Start of New Anti-Cancer Therapy as an Event		Ignoring Extended Loss to Follow-up and Start of New Anticancer therapy	
	Dabrafenib+ Trametinib (N=211)	Dabrafenib+ Placebo (N=212)	Dabrafenib+ Trametinib (N=211)	Dabrafenib+ Placebo (N=212)	Dabrafenib+ Trametinib (N=211)	Dabrafenib+Placebo (N=212)
Progressed or died (event)	103 (49%)	113 (53%)	108 (51%)	124 (58%)	105 (50%)	119 (56%)
Median (months) 95% CI	9.3 (7.7, 11.1)	7.6 (5.9, 10.9)	9.2 (7.5, 11.0)	7.2 (5.6, 9.1)	9.3 (7.7, 11.0)	7.6 (5.9, 9.7)
Adjusted hazard ratio Estimate 95% CI	0.73 (0.56, 0.96)		0.71 (0.55, 0.92)		0.73 (0.56, 0.96)	
Stratified log-rank p-value	0.021		0.008		0.019	

Subgroup analyses of overall survival and PFS

Results of the subgroups analyses were consistent with the results of the primary OS and PFS analyses.

Figure 10: Hazard ratios and 95% confidence intervals for OS subgroup analyses - Study MEK115306 (data cut-off date of 12 January 2015)

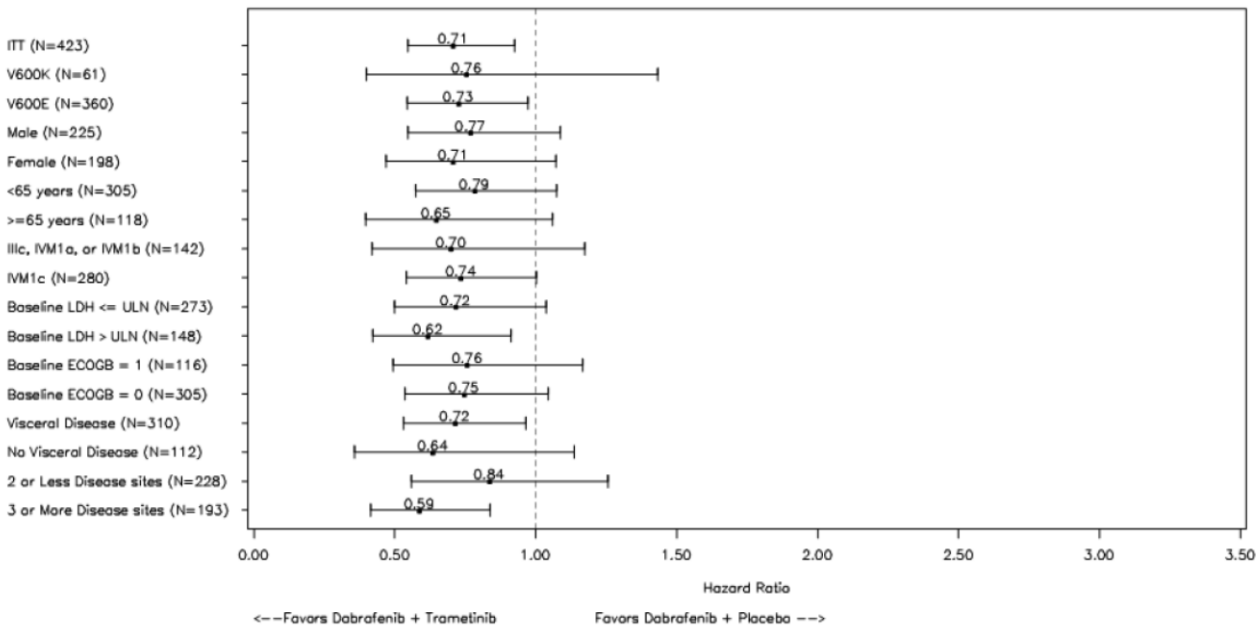
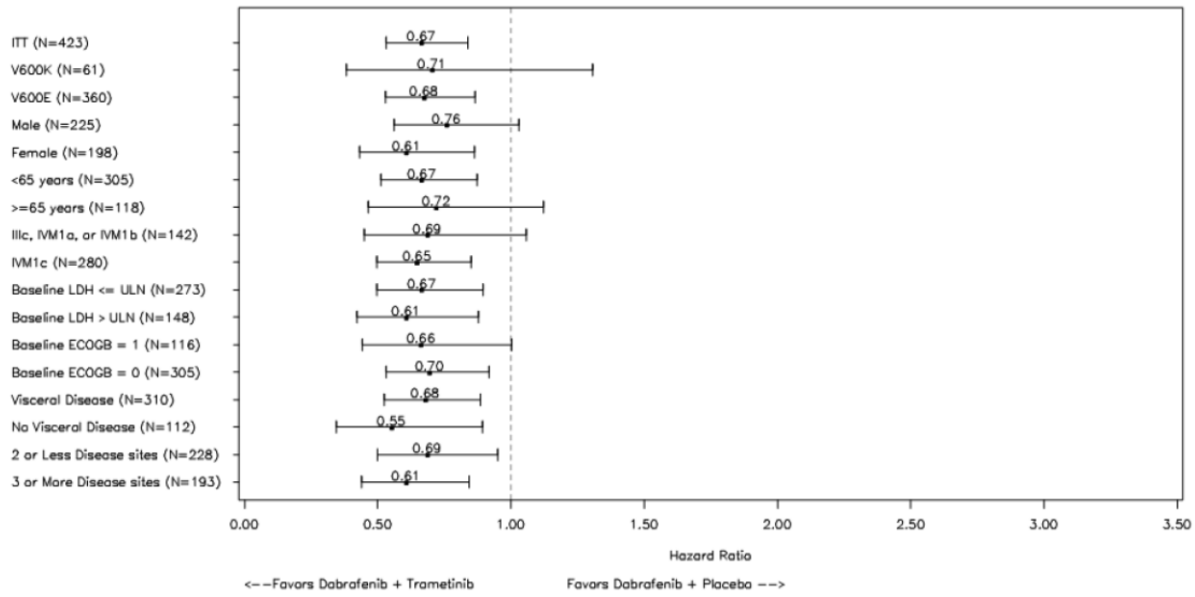


Figure 11: Hazard ratios and 95% confidence intervals for PFS subgroup analyses (data cut-off date of 12 January 2015)



Summary of main study

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

Title: MEK115306		
Study identifier	MEK115306	
Design	Study MEK115306 is a multi-centre, randomized, double-blind, active controlled Phase III study comparing dabrafenib 150 mg BID plus trametinib 2 mg QD versus dabrafenib 150 BID plus placebo in patients with histologically confirmed cutaneous melanoma which was either Stage IIIC or Stage IV and determined to be V600 mutation positive	
Hypothesis	The primary objective was to show superiority of the combination dabrafenib-trametinib versus dabrafenib monotherapy in terms of PFS	
Treatments groups	Test treatment	Dabrafenib (150 mg BID)+trametinib (2 mg QD), Patients are treated until progression, n= 211
	Control treatment	Dabrafenib (150 mg BID). Patients are treated until progression, n= 212
Endpoints and definitions	PFS	Investigator assessed Progressive free survival
	OS	Overall survival
	ORR	Investigator-assessed overall response rate (CR+PR)
	DOR	Duration of Response
Database lock	26 August 2013 (PFS) 12 January 2015 (OS)	

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat population		
Effect estimate per comparison	**2013-08-26 PFS**, investigator	dabrafenib + trametinib	dabrafenib + placebo
	Event rate	48%	51%
	HR	0.75	0.57; 0.99
	P-value	0.035	
	PFS, BICR		
	Event rate	44%	44%
	HR	0.78	0.59; 1.04
	P-value	0.085	
	OS		
	Event rate	19%	26%
	HR	0.63	0.42; 0.94
	P-value	0.023	
	ORR (BICR)	61%	47%
	Difference	15% (5%; 24%)	
	p-value	0.0024	
	2015-01-12 OS		
	Event rate	47%	58%
	HR	0.71	0.55; 0.92
	P-value	0.011	
	Median (estimated)	25.1 m	18.7 m
	PFS, investigator		
	Event rate	66%	76%
	HR	0.67	0.53; 0.84
	P-value	<0.001 (exploratory)	
	Median	11 m	9 m
	Comment	HR for PFS similar to HR for OS	

Descriptive statistics and estimate variability	Treatment group	Dabrafenib+trametinib	Dabrafenib monotherapy
	Number of subject	211	212
	Median PFS	11.0 months	8.8 months
	95% CI	8.0, 13.9	5.9, 9.3
	Median OS	25.1 months	18.7 months
	95% CI	19.2, NR	15.2, 23.7
	ORR	69%	53%
	95% CI	61.8, 74.8	46.3, 60.2
	Median DOR	12.9 months	10.6 months
	95% CI	9.4, 19.5	9.1, 13.8

Effect estimate per comparison	Primary endpoint: PFS	Comparison groups	Combination therapy/ monotherapy
		Estimated HR	0.67
		95% CI	0.53, 0.84
		P-value	P<0.001
	Secondary endpoint: OS	Comparison groups	Combination therapy/ monotherapy
		Estimated HR	0.71
		95% CI	0.55, 0.92

		stratified Log-Rank P-value	P= 0.011
	Secondary endpoint: ORR	Comparison groups	Difference in response rate
		CR+PR	15%
		95% CI	6.0, 24.5
		P-value	0.0014

Study MEK116513: A Phase III, randomised, open-label study comparing the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (stage IIIc) or metastatic (stage IV) BRAF V600E/K mutation positive cutaneous melanoma

Methods

Study participants

The MEK116513 study population included with histologically confirmed cutaneous melanoma that was either Stage IIIC (unresectable) or Stage IV (metastatic) and who were determined to be V600E or V600K mutation positive.

Key inclusion criteria were:

- ≥18 years of age
- Histologically confirmed, stage III unresectable (Stage IIIC) or metastatic (Stage IV) cutaneous melanoma, which is also determined to be BRAF V600E/K mutation-positive, using the bio Merieux investigational use only (IUO) THxID BRAF Assay. The assay was tested in a central reference laboratory. Patients with ocular or mucosal melanoma were not eligible.
- Measurable disease (i.e., present with a least one measurable lesion per RECIST, version 1.1.).
- All prior anti-cancer treatment-related toxicities (except alopecia and laboratory values as listed in Table 4) must have been ≤Grade 1
- An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate baseline organ function.

Key exclusion criteria included following:

- Any prior use of BRAF/MEK inhibitors, or ipilimumab in the advanced or metastatic setting
- Prior systemic anti-cancer treatment (chemotherapy, immunotherapy, biologic therapy, vaccine therapy, or investigational treatment) for stage IIIC (unresectable or Stage IV (metastatic) melanoma. Prior systemic treatment in the adjuvant setting was allowed. (Note: Ipilimumab treatment must have ended at least 8 weeks prior to randomization).
- Any major surgery, extensive radiotherapy, chemotherapy with delayed toxicity, biologic therapy, or immunotherapy within the last 21 days. Chemotherapy given daily or weekly without the potential for delayed toxicity within the last 14 days
- Taking an investigational drug within 28 days or 5 half-lives (minimum 14 days) whichever was shorter, prior to randomization.
- History of other malignancy. Patients who had been disease-free for 3 years or patients who had

a history of completely resected non-melanoma skin cancer were eligible

- Any serious and/or unstable pre-existing medical (aside from malignancy exception above), psychiatric disorder, or other conditions that could interfere with patient's safety, obtaining informed consent or compliance to the study procedures
- Known human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection
- Brain metastases with the following exceptions:
    - All known lesions must be previously treated with surgery or stereotactic radiosurgery (prior whole brain radiotherapy is not allowed), and
    - Brain lesion(s), if still present, must be confirmed stable (i.e. no increase in lesion size), for ≥12 weeks prior to randomization (stability must be confirmed with two consecutive MRI or CT scan with contrast, separated by > 6 weeks).
    - Asymptomatic with no corticosteroids requirement for ≥4 weeks prior to randomization, and
    - No enzyme-inducing anticonvulsants for ≥30 days prior to randomization
- History or evidence of cardiovascular risk
- Incorrectable electrolyte abnormalities (hyperkalemia, hypomagnesemia, hypocalcemia), long QT syndrome or taking medicinal products known to prolong the QT interval
- History or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR)

Treatments

Patients were randomized to receive dabrafenib 150 mg BID plus trametinib 2 mg daily or vemurafenib 960 mg BID.

Patients received study treatment until disease progression, death or unacceptable AE, including hematologic or other non-hematologic toxicity, and/or meeting stopping criteria for liver chemistry.

Furthermore, patients received full supportive care during the study, including transfusion of blood and blood products and treatment with antibiotics, anti-emetics, anti diarrhoeals and analgesics, as appropriate. Use of anticoagulants such as warfarin was permitted provided that international normalized ratio (INR was monitored in accordance with local institutional practice.

Objectives

The primary objective of study MEK116513 was to establish the superiority of dabrafenib and trametinib combination therapy over vemurafenib monotherapy with respect to overall survival (OS) for patients with advanced/metastatic BRAF V600E or V600K mutation-positive cutaneous melanoma.

The secondary objectives were to compare dabrafenib and trametinib combination therapy with vemurafenib monotherapy for the following:

- Progression-free survival (PFS)
- Overall response rate (ORR)

- Duration of response

Furthermore a secondary objective was to characterize the safety of dabrafenib and trametinib combination therapy, including incidences of squamous cell carcinoma (SCC) and other proliferative cutaneous lesions.

An exploratory objective was to evaluate and compare changes in health-related quality of life (HRQoL) of patients in the dabrafenib and trametinib combination therapy arm with those in the vemurafenib monotherapy arm.

Outcomes / endpoints

The primary endpoint of MEK116513 was Overall Survival, defined as the time from randomization until death due to any cause.

Secondary efficacy endpoints included PFS as defined as the time from randomization until the earliest date of disease progression by investigator per Response Evaluation Criteria In Solid Tumors v1.1 or death due to any cause; ORR as defined as the percentage of subjects with a confirmed complete response (CR) or partial response (PR) at any time per RECIST v1.1; Duration of response as defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause among subjects who achieved an overall response (i.e., confirmed CR or PR); ORR defined as the percentage of patients with a confirmed CR or PR at any time and Duration of response defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause among patients who achieved an overall response (i.e., confirmed CR or PR).

Disease progression and response evaluation were determined according to the definitions established in RECIST, version 1.1. At baseline, computed tomography (CT) scan of the chest/abdomen/pelvis or MRI of the abdomen/pelvis and any area of known disease, skin lesion photography, and clinical disease assessment for palpable lesions were performed. If clinically indicated a CT or MRI scan of affected bone areas was required at baseline. Lesions, if present, continued to be followed consistently throughout the study until disease progression, death or withdrawal of consent.

At each post-baseline assessment (Week 8 and every 8 week thereafter through Week 56 and then every 12 weeks thereafter), evaluation of the sites of disease identified by these scans and/or by medical photography or direct measurement was required. If the last radiographic assessment was more than 8 weeks prior to study withdrawal and progressive disease (PD) had not been documented, a disease assessment was obtained at the time of withdrawal.

All patients who permanently discontinued dabrafenib + trametinib or vemurafenib without disease progression continued to radiographic disease assessment according to the study protocol until disease progression, death or withdrawal of consent, whichever was documented first. In addition, all patients who permanently discontinued study treatment were followed for survival and new anti-cancer therapy. Follow-up continued until study completion/withdrawal or death, whichever occurred first.

Other secondary endpoints included, safety measurement by assessment of AEs, clinical assessment including vital signs and physical examination, ocular examination, 12-lead electrocardiograms (ECG), echocardiogram (ECHO), chemistry and hematology laboratory values.

Health-related quality of life measures were assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, the EuroQol-5D and the melanoma subscale of the Functional Assessment of Cancer Therapy- Melanoma.

Sample size

Under the assumptions that PFS was exponentially distributed, 1:1 randomization, 0.05 type I error, the study needed 288 deaths in the final analysis to detect a HR= 0.675 with 90% power (median OS times of 13.5 and 20 months in the vemurafenib arm and the combination therapy arm, respectively). Given an accrual rate of 18 subjects per month over the first 6 months, and 75 subjects per month thereafter resulting in enrollment duration of approximately 13 months, an estimated total of 694 subjects (i.e., 347 subjects in each of the arms) would need to be enrolled.

Randomisation

Before randomization eligible patients were stratified by LDH (above ULN vs. equal to or below ULN) and BRAF mutation (V600E versus V600K). Patients with both V600E and V600K mutations were included in the V600K count for the stratification.

Patients were centrally randomized (randomized phase) through the Registration and Medication Ordering System (RAMOS) (Interactive Voice Response System [IVRS]) in a 1:1 ratio to receive either dabrafenib and trametinib combination therapy or vemurafenib monotherapy.

Blinding (masking)

This study was designed as an open-label study.

Statistical methods

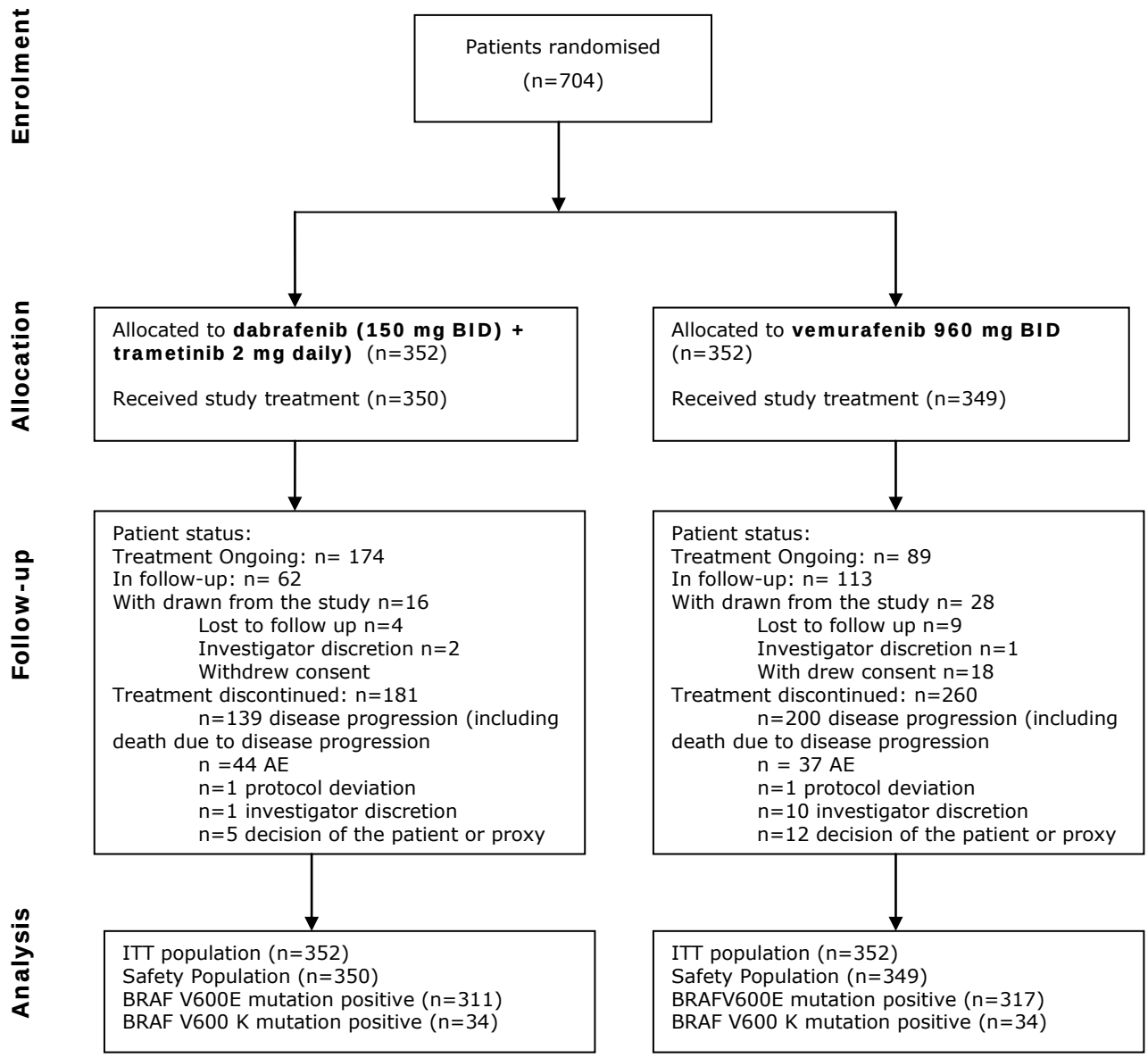
Overall survival was summarized using the Kaplan-Meier method, and survival curves were compared between treatment arms using a stratified log-rank test stratifying for BRAF mutation status (V600E versus V600K) and baseline LDH (>ULN versus ≤ULN).

The statistical methods were the same as in study 115306 with the following alterations:

- OS (instead of PFS) was primary; no multiplicity for secondary endpoints (such as PFS, ORR)
- interim analysis OS at 70% of required events (i.e., 202 of the 288 events for the final OS analysis) with Lan and DeMets version of the O'Brien-Fleming alpha-spending function for efficacy and a Rho beta-spending function (Rho = 3) for futility:
    a) 70% of expected events: α =0.007 (one-sided)
        - stop for efficacy if one-sided p-value <0.0074 (HR<0.6992);
        - stop for futility if one-sided p-value >0.1733 (HR>0.8710)
    b) 100% of expected events: α=0.025 (one-sided)
        - claim success if one-sided p-value <0.0228 (HR<0.7822)

Results

Participant flow



Recruitment

A total of 704 patients were enrolled in 28 countries. Of the 28 countries, France (101 patients) and Germany 81 patients) enrolled the largest number of patients.

Conduct of the study

The original study protocol dated 15 March 2012 was amended 4 times. The main changes to the protocol were as follows:

- Amendment 01: included new requirements for subjects that remained on study treatment after radiographic disease progression, required treatment interruption for any treatment-related AE of grade 3, required that rash of grade ≥3 must resolve to grade ≤1 before study treatment could resume, enhanced monitoring for ophthalmic toxicities and some additional changes to the eligibility criteria and clarification to the protocol in relation to safety

- Amendment 03: changes to the protocol included revision of table for dose modifications for LVEF decrease, monitoring guidelines for new cutaneous and non-cutaneous malignancies and revisions to clarify the guidance on the management of patients and ADRs during the study.

- Amendment 04: revision to the management and dose modification guidelines for particular ADRs and added new guideline for pancreatitis and hyperglycaemia.

The study was stopped early as the adjusted stopping boundary for efficacy at the interim analysis ($p<0.0214$) was crossed and the study was stopped for efficacy by the IDMC.

Baseline data

Table 18: Demographics and baseline disease characteristics (ITT population) - Study MEK116513

	Dabrafenib + Trametinib (N=352)	Vemurafenib (N=352)	Total (N=704)
Age (y), n (%)			
Mean (SD)	54.1 (13.83)	54.3 (14.06)	54.2 (13.94)
Median (Minimum, Maximum)	55.0 (18, 91)	54.0 (18, 88)	54.5 (18, 91)
Age Group (y), n (%)			
<65	274 (78)	264 (75)	538 (76)
≥65	78 (22)	88 (25)	166 (24)
N (Safety Population)	350	349	699
<75	329 (94)	323 (93)	652 (93)
≥75	21 (6)	26 (7)	47 (7)
Sex, n (%)			
Female	144 (41)	172 (49)	316 (45)
Male	208 (59)	180 (51)	388 (55)
Measurable Disease at Baseline, n (%)			
Yes	351 (>99)	350 (>99)	701 (>99)
No	0	2 (<1)	2 (<1)
Prior Immunotherapy (adjuvant setting), n (%)			
Yes	61 (17)	93 (26)	154 (22)
No	291 (83)	259 (74)	550 (78)
ECOG PS at Baseline, n (%)			
1	102 (29)	104 (30)	206 (29)
0	248 (70)	248 (70)	496 (70)
BRAF Mutation Status [a, b], n (%)			
V600E	312 (89)	317 (90)	629 (89)
V600K	34 (10)	34 (10)	68 (10)
V600E & V600K	5 (1)	1 (<1)	6 (<1)
Stage at Screening, n (%)			
Stage IVM1c	221 (63)	208 (59)	429 (61)
Stage IIIc, IVM1a, or IVM1b	130 (37)	143 (41)	273 (39)
(M stage) at Screening, n (%)			
M0	14 (4)	26 (7)	40 (6)
M1a	55 (16)	50 (14)	105 (15)
M1b	61 (17)	67 (19)	128 (18)
M1c	221 (63)	208 (59)	429 (61)
Unknown	0	1 (<1)	1 (<1)
Baseline LDH [a], n (%)			
<ULN	118 (34)	114 (32)	232 (33)
≤ULN	233 (66)	238 (68)	471 (67)
Visceral Disease at Baseline, n (%)			
Yes	278 (79)	271 (77)	549 (78)
No	73 (21)	81 (23)	154 (22)
Number of Disease Sites at Baseline, n (%)			
<3 sites	177 (50)	201 (57)	378 (54)
≥3 sites	174 (49)	151 (43)	325 (46)

Abbreviations: ECOG PS=Eastern Cooperative Oncology Group performance status; LDH=lactate dehydrogenase; ULN=upper limit of normal; y=years
a. Data are from eCRF, while stratification factors were based upon randomized strata from the Registration and Medication Ordering System. Baseline LDH and BRAF mutation status collected in CRF were summarized
b. The one subject with wildtype BRAF was not included in this summary and was excluded from all subgroup analyses for BRAF mutation status

Table 19: Prior anti-Cancer therapy (ITT population) - Study MEK116513

	Dabrafenib + Trametinib (N=352)	Vemurafenib (N=352)	Total (N=704)
Subjects with any therapy [a], n (%)	309 (88)	318 (90)	627 (89)
Chemotherapy	13 (4)	6 (2)	19 (3)
Immunotherapy	61 (17)	93 (26)	154 (22)
Biologic therapy	1 (<1)	5 (1)	6 (<1)
Surgery	302 (86)	310 (88)	612 (87)
Radiotherapy	53 (15)	61 (17)	114 (16)

Data Source: Table 1.7023

a. Subjects may have received more than 1 type of anti-cancer therapy.

Numbers analysed

All 704 randomized patients were included in the ITT population. The majority of patients (89%) had BRAF V600E mutation-positive melanoma. BRAF V600E and BRAF V600K mutation-positive populations are subsets of the ITT population. These subsets do not include the 6 patients with both V600E and V600K, or the 1 patient with wild type BRAF.

Outcomes and estimation

Primary endpoint: Overall survival

The results for OS are presented in Table 20. Median OS has not been reached in the combination therapy arm and was 17.2 months in the vemurafenib monotherapy arm with a HR of 0.69 (95% CI: 0.53, 0.89; p=0.005).

The median follow-up time (defined as time from randomization to death or last contact) was 11.0 months in the combination therapy arm and 10.0 months in the vemurafenib monotherapy arm.

Table 20: Overall Survival (ITT Population) - Study MEK116513

	Dabrafenib + Trametinib (N=352)	Vemurafenib (N=352)
Number of Subjects, n (%)		
Died (event)	100 (28)	122 (35)
Censored, follow-up ended	16 (5)	28 (8)
Censored, follow-up ongoing	236 (67)	202 (57)
Estimates for Overall Survival (months)		
1st Quartile (95% CI)	10.9 (9.3, 13.8)	8.9 (7.8, 10.4)
Median (95% CI)	NR (18.3, NR)	17.2 (16.4, NR)
3rd Quartile (95% CI)	NR (NR, NR)	NR (18.0, NR)
Adjusted Hazard Ratio [a]		
Estimate (95% CI)	0.69 (0.53, 0.89)	
Stratified Log-Rank P-Value	p=0.005	

Data Source: Table 2.1010

Abbreviations: LDH=lactate dehydrogenase; NR=not reached

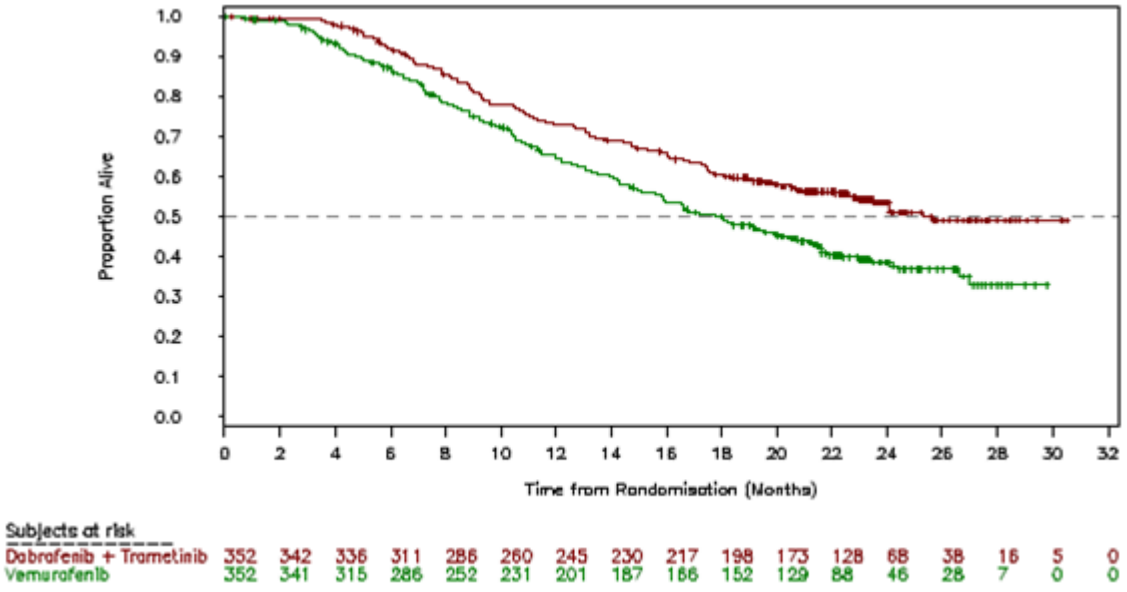
a. A hazard ratio <1 indicates a lower risk with dabrafenib + trametinib compared with vemurafenib. Hazard Ratio and p-value from stratified log-rank test are adjusted for randomized strata: baseline LDH and BRAF mutation status.

Table 21: Updated OS analysis – Study MEK116513

		MEK116513 Updated OS analysis (13 March 2015)	
		Dabrafenib + Trametinib	Vemurafenib
ITT population	N	352	352
	Died	155 (44%)	194 (55%)
	Censored, follow-up ended	21 (6%)	39 (11%)
	Censored, follow-up ongoing	176 (50%)	119 (34%)
	Median (95% CI)	25.6 (22.6, NR)	18.0 (15.6, 20.7)
	Adjusted Hazard Ratio Estimate (95% CI)	0.66 (0.53, 0.81)	
	Stratified[a] Log-Rank P-value (2-sided)	<0.001	

[a] Log-rank test is stratified by baseline LDH and BRAF mutation status.

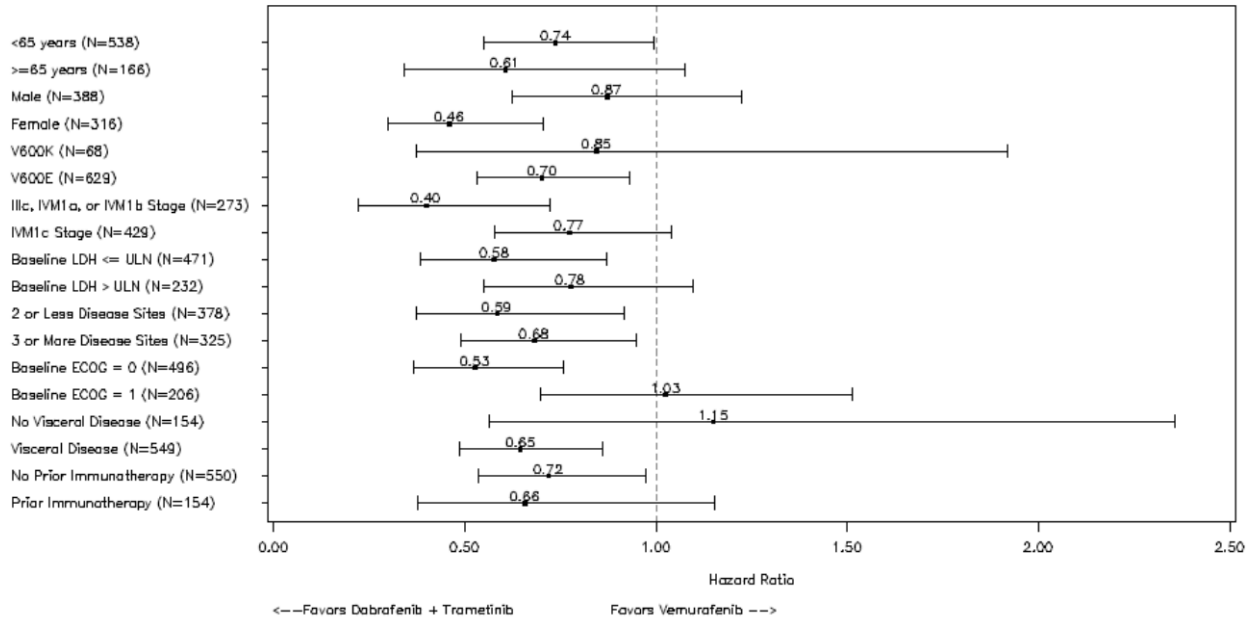
Figure 12: Kaplan-Meier updated overall survival estimate – Study MEK116513



Ancillary analyses

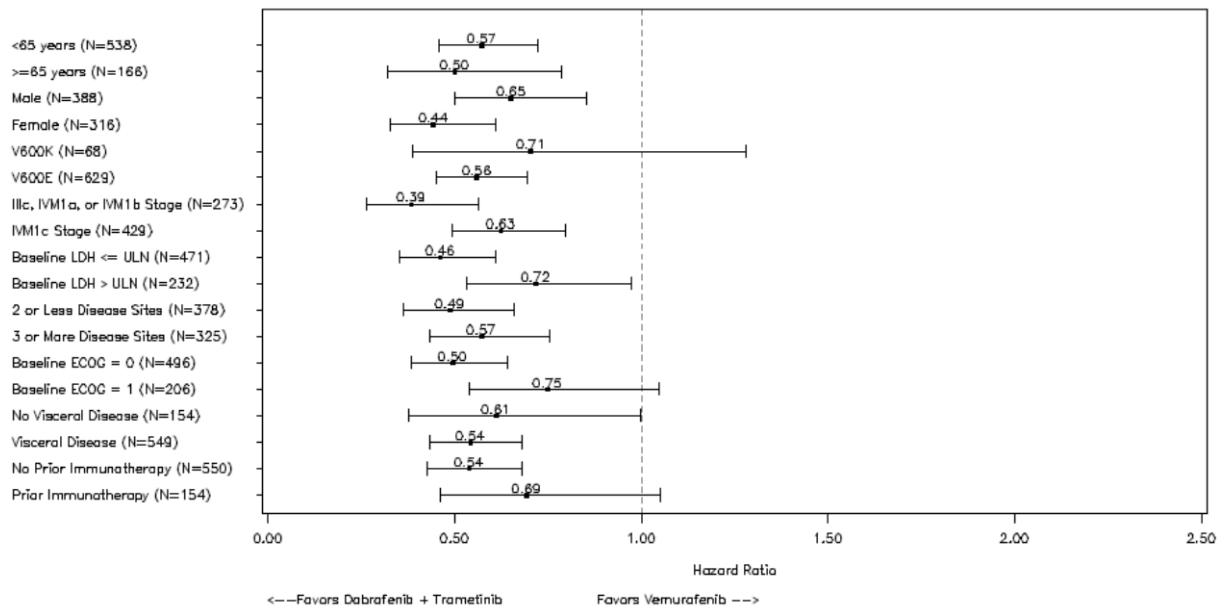
Overall Survival

Figure 13: Hazard Ratios and 95% Confidence Intervals for Overall Survival Subgroup Analyses (ITT Population) – Study MEK116513



Progression Free Survival

Figure 14: Hazard Ratios and 95% Confidence Intervals for Progression-Free Subgroup Analyses (ITT Population) – Study MEK116513



Overall Response Rate

Table 22: Investigator-Assessed Best Response (With Confirmation) (RECIST v1.1 Criteria) by Prognostic Factors (Subjects with Measurable Disease at Baseline in ITT Population) – Study MEK116513

	Dabrafenib + Trametinib (N=351)	Vemurafenib (N=350)
Overall (CR+PR), n/N (%)	226/351 (64)	180/350 (51)
BRAF mutation status, n/N (%)		
V600E	200/311 (64)	165/315 (52)
V600K	22/ 34 (65)	15/ 34 (44)
LDH level, n/N (%)		
LDH ≤ULN	168/232 (72)	139/236 (59)
LDH >ULN	57/118 (48)	41/114 (36)
Sex, n/N (%)		
Male	129/207 (62)	90/180 (50)
Female	97/144 (67)	90/170 (53)
Age group, n/N (%)		
<65 years old	175/274 (64)	130/262 (50)
≥65 years old	51/ 77 (66)	50/ 88 (57)

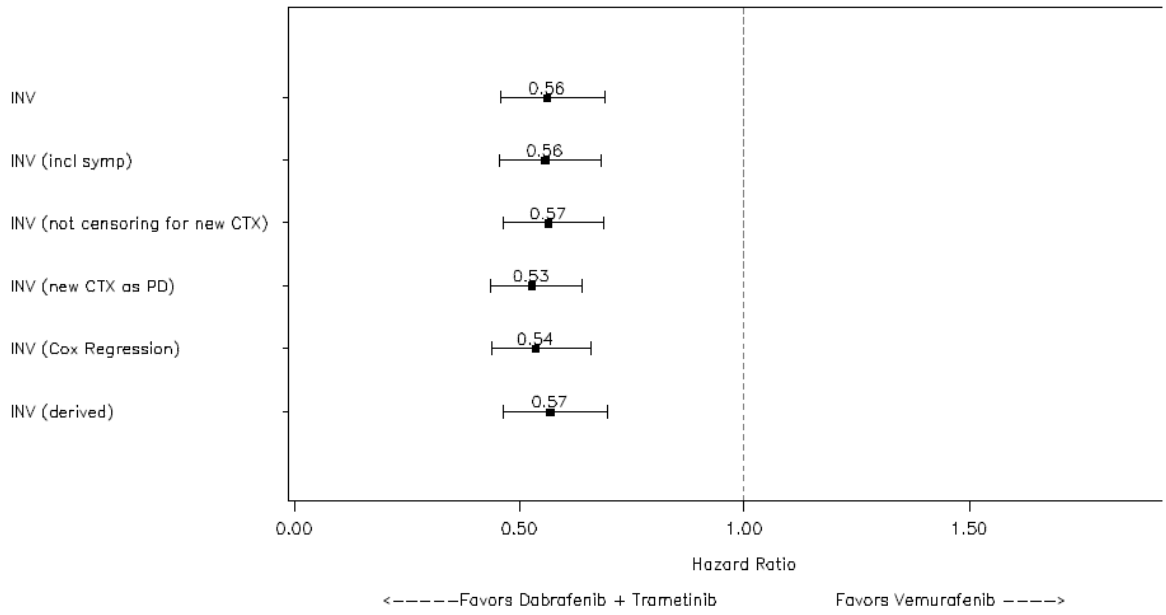
Sensitivity analysis

The following sensitivity analyses were conducted for PFS by investigator assessment:

- Symptomatic progression as events
- Considering start of new anti-cancer therapy as an event
- Considering radiological progression after extended loss to follow-up and start of new anti-cancer therapy as an event
- Cox regression proportional hazards regression model
- Using derived responses from investigator lesion assessments.

Results of the sensitivity analyses were consistent with the result observed for the overall ITT analysis.

Figure 15: Hazard Ratios and 95% Confidence Intervals for Progression-Free Survival analyses (ITT population) – Study MEK116513



Data Source: Figure 12.2010
Abbreviations: INV=investigator; incl symp=symptomatic progressions as events; CTX=anti-cancer therapy; PD=progressive disease

Summary of main study

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

Title: MEK116513		
Study identifier	MEK116513	
Design	MEK116513 is a two arm, open-label randomized, phase III study comparing dabrafenib and trametinib combination therapy with vemurafenib monotherapy in patients with histologically confirmed cutaneous melanoma which was either Stage IIIC or Stage IV and determined to be V600 mutation positive	
Hypothesis	The primary objective was to establish the superiority of dabrafenib and trametinib combination therapy over vemurafenib monotherapy with respect to overall survival	
Treatments groups	Test treatment	Dabrafenib (150 mg BID)+trametinib (2 mg QD), Patients are treated until progression, n=350
	Control treatment	Vemurafenib (960 mg BID), Patients are treated until progression, n=349
Endpoints and definitions	OS	Overall survival
	PFS	Investigator assessed Progressive free survival
	ORR	Investigator-assessed overall response rate (CR+PR)
	DOR	Duration of Response

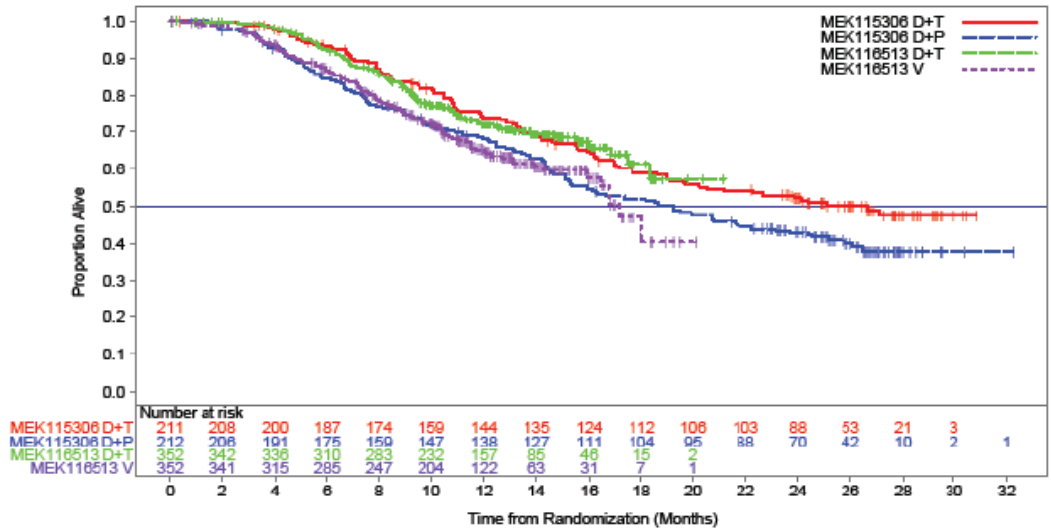
Database lock	17 April 2014: OS interim at 222/704 (32%) event rate, IDMC recommended closure		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat population		
Descriptive statistics and estimate variability	Treatment group	dabrafenib+trametinib	Vemurafenib monotherapy
	Number of subject	352	352
	Median OS	25.6	18 months
	95% CI	22.6, NR	15.6, 20.7
	Median PFS	11.4 months	7.3 months
	95% CI	9.9, 14.9	5.8, 7.8
	ORR	64%	51%
	95% CI	59.1, 69.4	46.1, 56.8
	Median DOR	13.8 months	7.5 months
	95% CI	11.0, NR	7.3, 9.3
Effect estimate per comparison	Primary endpoint: OS	Comparison groups	Combination therapy/monotherapy
		Estimate HR	0.66
		95% CI	0.53, 0.81
		P-value	P<0.001
	Secondary endpoint: PFS	Comparison groups	Combination therapy/monotherapy
		Estimate HR	0.56
		95% CI	0.46, 0.69
		P-value	<0.001
	Secondary endpoint: ORR	Comparison groups	Difference in response rate
		Difference in response rate	13%
		95% CI	5.7, 20.2
		P-value	P=0.0005

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

Overall survival

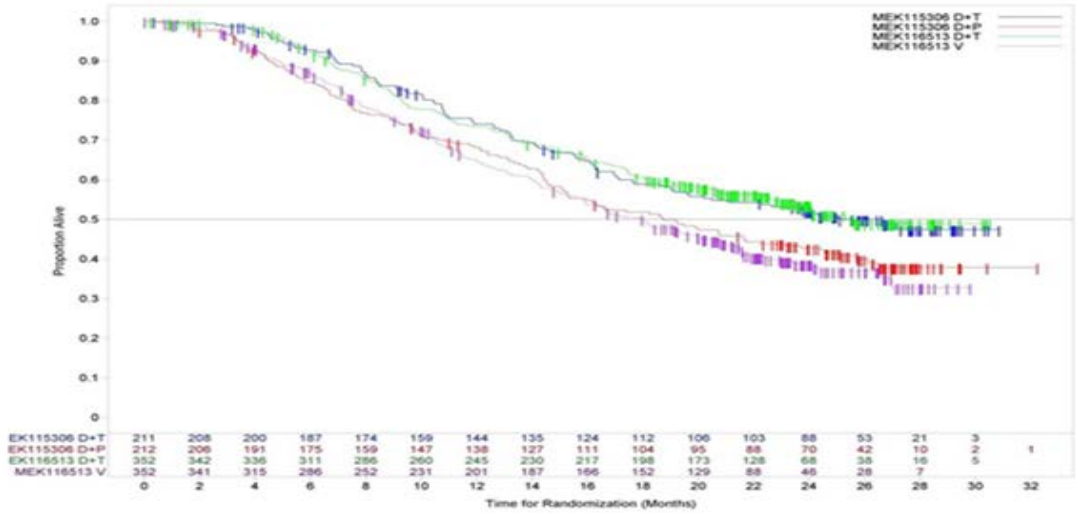
The Kaplan-Meier curves for OS representing the combination arms for study MEK115306 (final data cut: 12 January 2015) and study MEK116513 (original data cut: 17 April 2014) are presented in Figure 16. An updated analysis is presented in Figure 17.

Figure 16: Kaplan-Meier Overall Survival curves (MEK115306 and MEK116513 ITT Populations)



Abbreviations: D+T=combination dabrafenib and trametinib; D+P=dabrafenib and placebo; V=vemurafenib

Figure 17: Kaplan-Meier Overall Survival curves (MEK115306 and MEK116513 ITT Populations) (update data cut-off: 13 March 2015)



Analysis of follow-up anti-cancer therapy showed that in both studies MEK115306 and MEK116513, more patients in the BRAF inhibitor monothearpy arms (51% and 43%) received follow-up anti-cancer therapy

including ipilumuamb and pembrolizumab, compared with the combination therapy arms (33% and 20%).

Table 23: Post-progression study treatment and select follow-up anti-cancer therapies (MEK115306 and MEK116513 ITT Populations)

	MEK115306		MEK116513	
	Dabrafenib + Trametinib (N=211)	Dabrafenib + Placebo (N=212)	Dabrafenib + Trametinib (N=352)	Vemurafenib (N=352)
Post-progression study treatment				
Received study treatment for at least 15 days after disease progression	62 (29)	65 (31)	80 (23)	81 (23)
Follow-up anti-cancer therapy[a]				
Any follow-up anti-cancer therapy	70 (33)	108 (51)	72 (20)	152 (43)
Ipilimumab[b]	37 (18)	59 (28)	41 (12)	78 (22)
Pembrolizumab	5 (2)	11 (5)	4 (1)	10 (3)
Nivolumab	1 (<1)	3 (1)	0	2 (<1)

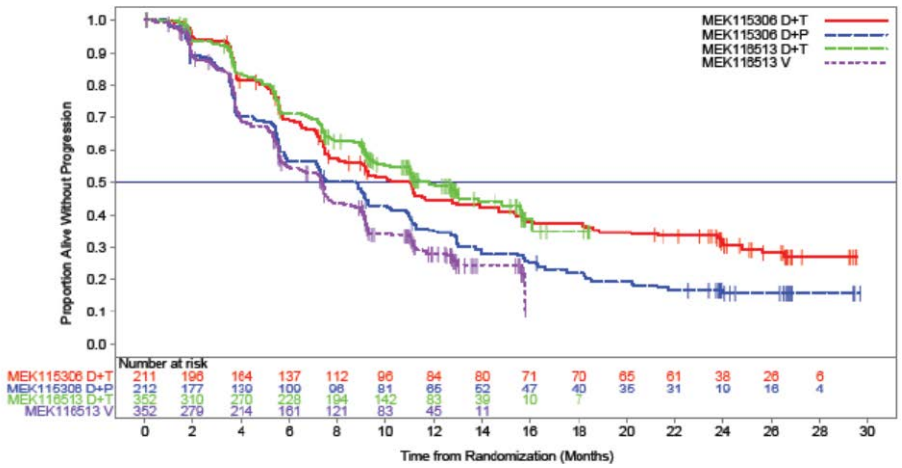
a. Study treatment is not included as follow-up therapy.
b. Ipilimumab was the most commonly administered follow-up anti-cancer therapy in the combination and BRAF-inhibitor monotherapy arms in both studies.

Progression Free Survival

The Kaplan-Meier curves for PFS representing the combination arms for study MEK115306 and study MEK116513 are presented in Figure 18. The median PFS for the combination arms was approximately 11 months.

The median for the combination therapy arm of MEK115306 with additional duration of follow-up and additional events was consistent with that of Study MEK116513 (11.0 months and 11.4 months respectively).

Figure 18: Investigator-Assessed Kaplan-Meier PFS Curves (MEK115306 and MEK116513 ITT populations)



Abbreviations: D+T=combination dabrafenib and trametinib; D+P=dabrafenib and placebo; V=vemurafenib

Overall Response Rate and Duration of response

The overall response rates and duration of responses were reasonably consistent between the three studies.

Table 24: Investigator-assessed best confirmed response rate and duration of response in subjects with measurable disease at baseline (by RECIST v1.1) (MEK115306, MEK116513, and BRF113220 Part C ITT Populations)

	MEK115306		MEK116513		BRF113220 Part C	
	Dabrafenib + Trametinib (N=210)	Dabrafenib + Placebo (N=210)	Dabrafenib + Trametinib (N=351)	Vemurafenib (N=350)	Dabrafenib + Trametinib (N=54)	Dabrafenib Monotherapy (N=54)
Best response, n (%)						
Complete response	33 (16)	28 (13)	47 (13)	27 (8)	5 (9)	2 (4)
Partial response	111 (53)	84 (40)	179 (51)	153 (44)	36 (67)	27 (50)
Stable disease	50 (24)	66 (31)	92 (26)	106 (30)	13 (24)	22 (41)
Progressive disease	13 (6)	19 (9)	22 (6)	38 (11)	0	3 (6)
Not evaluable	3 (1)	13 (6)	11 (3)	26 (7)	0	0
Response rate						
CR+PR, n (%)	144 (69)	112 (53)	226 (64)	180 (51)	41 (76)	29 (54)
95% CI	(61.8, 74.8)	(46.3, 60.2)	(59.1, 69.4)	(46.1, 56.8)	(62.4, 86.5)	(39.6, 67.4)
Difference in response rate (combination – monotherapy) [a]						
CR+PR (%)	15		13		22	
95% CI for difference	(6.0, 24.5)		(5.7, 20.2)		(2.5, 40.7)	
p-value	0.001		<0.001		0.026	
Duration of response (months)						
n	144	113	226	181	41	29
Progressed or died (event), n (%)	86 (60)	79 (70)	89 (39)	93 (51)	21 (51)	25 (86)
Median	12.9	10.6	13.8	7.5	10.5	5.6
95% CI	(9.4, 19.5)	(9.1, 13.8)	(11.0, NR)	(7.3, 9.3)	(7.4, 14.9)	(4.5, 7.4)

Abbreviations: CR=complete response; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumours
a. Note that the difference in response rates was calculated prior to rounding the response rates to whole numbers

Health related Quality of Life

The health-related quality of life analyses in both Phase III studies are presented in Figure 19 and 20. Health related quality of life was not collected in Study BRF113220 Part C.

Figure 19: Change from baseline in global health status (ITT Population) – Study MEK115306

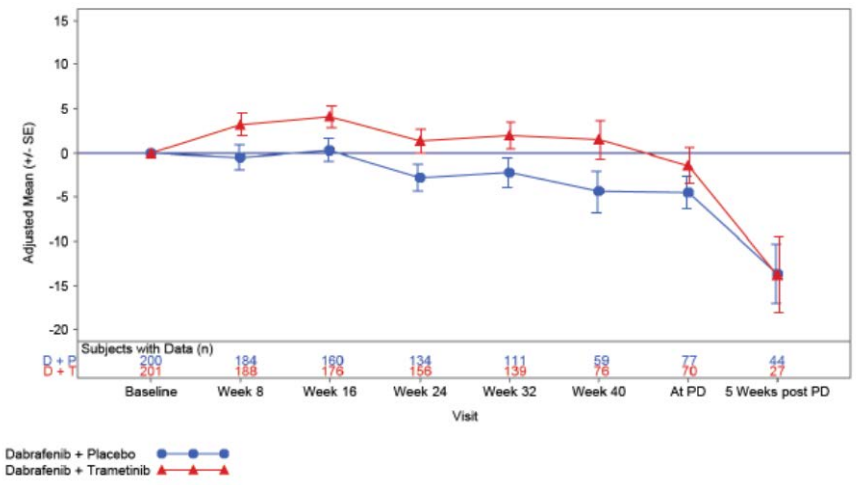
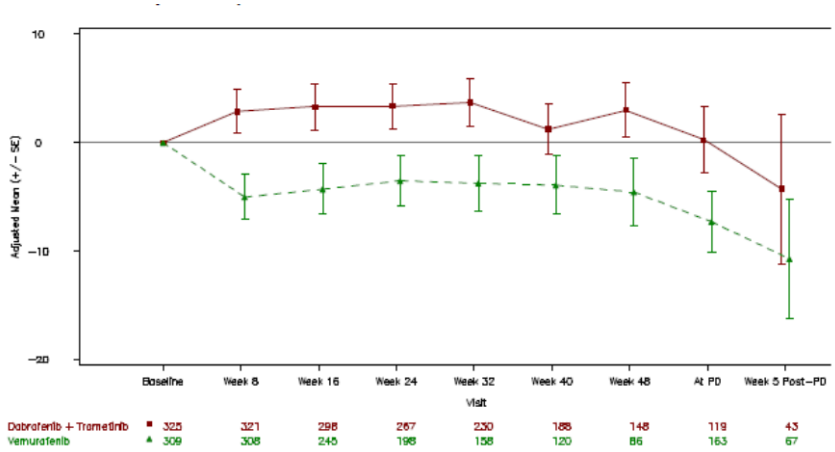


Figure 20: Change from baseline in global health status (ITT Population) – Study MEK116513



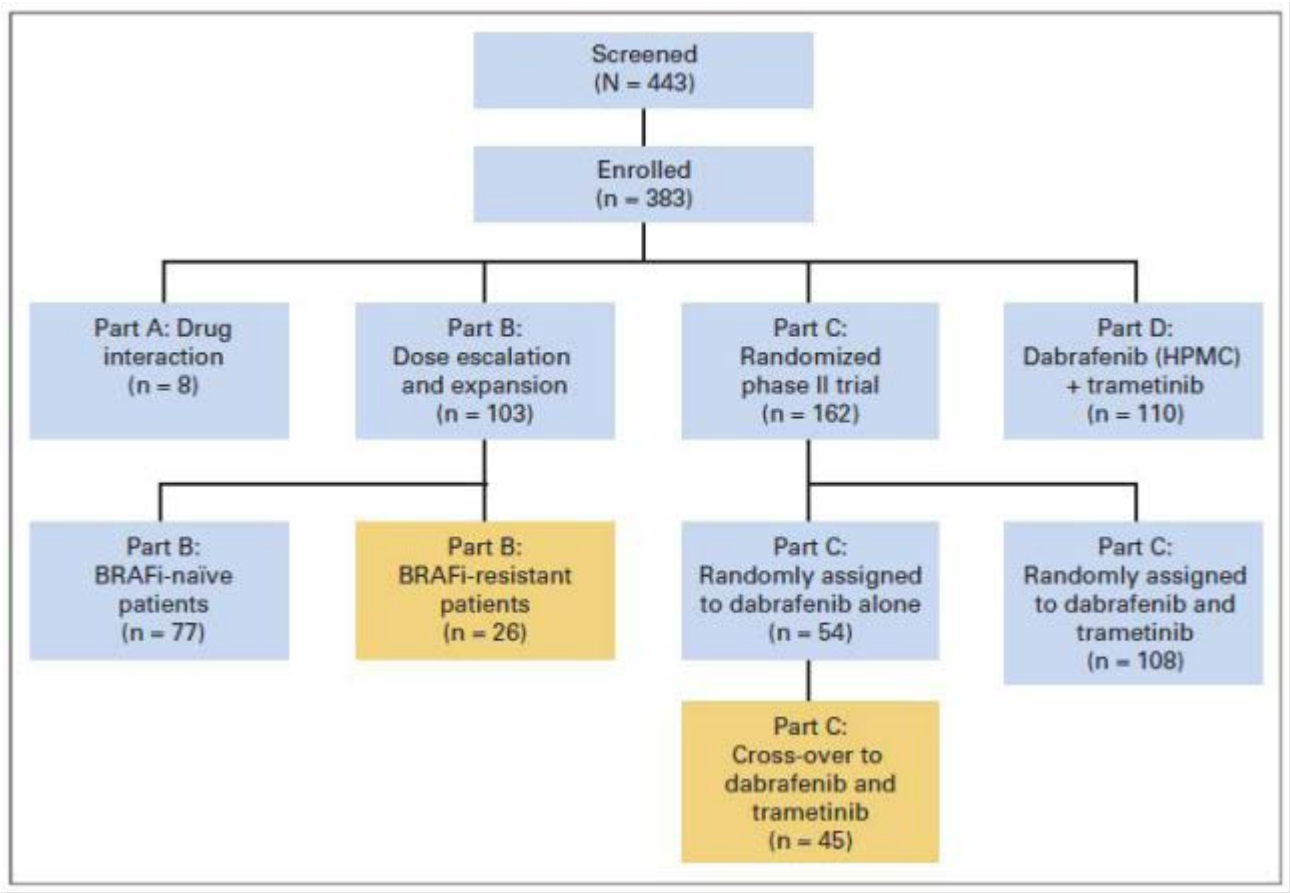
Abbreviations: ITT=intent-to-treat; PD=progressive disease

Supportive study(ies)

The study BRF113220 is was an open-label 4 part study designed to assess the safety, clinical efficacy, and pharmacokinetic activity of combination therapy with dabrafenib and trametinib. Part B of this study evaluated the safety and efficacy of escalating doses of dabrafenib (75 and 150 mg twice daily) and trametinib (1, 1.5, and 2 mg once daily) and 26 patients had a prior BRAFi therapy. Part C was a randomized, three-arm portion of the study where patients were assigned at a ratio of 1:1:1 to receive dabrafenib 150 mg twice daily as monotherapy or in combination with either trametinib 1mg once daily or 2mg once daily; 45 patients were randomized to dabrafenib monotherapy and subsequently crossed over to the combination therapy.

BRF113220 Part C was considered a supportive study for the proposed indication for the combination of trametinib and dabrafenib. Data on response rate and PFS have been previously presented in the pharmacology section as well as the dose response section. The combination of dabrafenib and trametinib has demonstrated limited efficacy in patients who have progressed after a prior BRAFi monotherapy in study BRF113220.

The efficacy of combination therapy with dabrafenib and trametinib for patients previously treated with a BRAFi alone before enrolment (BRAFi – resistant portion of part B) and for those who received dabrafenib monotherapy in this study who then crossed over to combination therapy at disease progression (cross-over portion of part C) were assessed.



The efficacy of combination therapy with dabrafenib and trametinib for patients previously treated with a BRAF inhibitor alone before enrolment (BRAFi – resistant portion of part B) and for those who received dabrafenib monotherapy in this study who then crossed over to combination therapy at disease progression (cross-over portion of part C) were assessed.

Patients from Part B had a confirmed response rate of 15% (4/26) and in Part C the patients who crossed over after progression on dabrafenib monotherapy had a confirmed response rate of 13% (6/45). Median progression free survival was 3.6 months for both parts (Part B 95% CI 2-5 m and Part C 95% CI 2-4m).
There were 22 patients receiving dabrafenib monotherapy for <6 months and 23 patients receiving dabrafenib from ⩾6 months.
Patients that had been treated with dabrafenib monotherapy for ⩾ 6 months prior to developing progressive disease, had a better clinical outcome with the combination of dabrafenib and trametinib where response rate of 26% with a median PFS of 3.9 months (95% CI, 3-7m) for patients treated longer than 6 months compared to response rate of 0% and median PFS of 1.8 months (95% CI, 2-4m) for patients who rapidly progressed in less than 6 months on their prior dabrafenib monotherapy.

2.4.4. Discussion on clinical efficacy

Design and conduct of clinical studies
The MEK115306 study was a randomized controlled phase III study. Progression free survival was the primary efficacy endpoint whereas OS was a secondary endpoint. The design and conduct of the study were considered acceptable. The CHMP noted that there was an over-enrolment of almost a quarter of the

planned study size. To assess whether the key results were possibly impacted because of the over enrolment, the MAH provided an analysis on the original sample size (i.e., a PFS-analysis timed at the 155 PFS event of the first 340 recruited patients) and the data confirmed the statistically significant PFS benefit of combination therapy when compared with monotherapy BRAF inhibitor in the original dataset as planned in the SAP.

The MEK116513 study was an open-label randomized Phase III study comparing dabrafenib and trametinib combination therapy with vemurafenib monotherapy. The primary endpoint of this study was OS and no cross over was allowed following discontinuation. Only 12 patients of the vemurafenib monotherapy arm and 5 of the patients in the combination arm discontinued treatment upon decision of the patient, suggesting that the open label design did not introduce a bias to the study results. Other systemic therapies were only allowed after study treatment discontinuation. The design and conduct of the study were considered acceptable.

The patient population included in the MEK115306 study and the MEK116513 study were comparable. The demographic characteristics and baseline characteristics for the treatment arm in study MEK115306 and in study MEK116513 were reasonably balanced, with the exception of a higher occurrence of visceral disease in the combination therapy arm compared with the dabrafenib monotherapy arm in the study MEK115306 and more patients with >3 sites in the combination arm compared with the vemurafenib arm in the study MEK116513. However, these imbalances did not affect the reliability of the study results. The stratification factors of LDH≤ ULN versus LDH>ULN and V600E versus V600K, the treatment arms were considered balanced.

Efficacy data and additional analyses

MEK115306

In the updated PFS analysis submitted with the application, 71.2% of the events for the PFS analysis (by investigator) had occurred. The HR= 0.67 (95% CI 0.53, 0.84; p<0.001) was in favour of the combination therapy with a median PFS of 11.0 months compared with 8.8 months for the monotherapy dabrafenib.

In the final OS analysis, 47% of the patients in the combination arm had died whereas 58% of the patients in dabrafenib monotherapy arm had died. For the whole study population, 52.4% of the death events had occurred and thus the OS data could be considered reasonably mature. The Kaplan-Meier curves for overall survival separated between the 2 and 3 months and remained separate until 24 months of follow up. The median OS for the combination therapy was 25.1 months and for monotherapy dabrafenib was 18.7 months with a HR of 0.71, (95% CI: 0.55, 0.92, p=0.011). The difference in OS of 6.4 months for the combination therapy was statistically significant and is considered clinically relevant.

The reported overall response rate (ORR; CR and PR) for the combination arm was higher than the ORR for the monotherapy arm (69% vs 53%, respectively), suggesting a higher anti-tumour activity with the combination treatment.

MEK116513

At the time of data lock point, the median time of follow up was above 10 months. The Kaplan-Meier OS curves separated early in the 3 to 4 month range and remained separate throughout the time of median follow-up. The median OS was 18.0 months for vemurafenib and was 25.6 months for the combination treatment with an estimate HR=0.66 (95% CI: 0.53, 0.81; p<0.001) which was statistically significant. The updated OS analysis for Study MEK116513 was based on 349 (50%) of events, which is very similar to the final OS analysis for Study MEK115306, which was based on 222 events (52%). The median PFS for the combination therapy was 11.4 months compared to 7.3 months for monotherapy with a HR=0.56 (95% CI: 0.46, 0.69; p<0.001) that was statistically significant.

The OS data for the combination therapy dabrafenib and trametinib obtained in studies MEK115306 and MEK116513 were comparable to each other. The OS results of the phase II study BRF113220 part C were supportive and showed a slightly shorter survival for patients treated with dabrafenib and trametinib combination therapy.

The PFS results were consistent with the positive OS results for the combination therapy, which are less susceptible for performance and assessment bias than PFS results.

The ORR was higher for the combination arm than for the monotherapy arms for both studies MEK116513 study and study BRF113220 Part C (MEK116513; 64% vs 51% and BRF113220 76% vs 54%, respectively) suggesting a higher anti-tumour activity with the combination treatment.

The QoL assessment shows for both phase III studies, at least until disease progression, a better health related quality of life for patients treated with dabrafenib+trametinib than for patients treated with a BRAF inhibitor monotherapy.

Subgroup analyses

No PFS or OS subgroup analysis was conducted for patients with a history of brain metastasis. Due to the strict inclusion and exclusion criteria of the studies, fewer than 20 patients with a history of brain metastases were treated in the clinical trials. Therefore the efficacy of combination therapy for patients with a history of brain metastasis in not known and a statement in the SmPC in section 4.4 and 5.1 has been included to inform the prescriber of the lack of data in this patient population. In addition, the effect of the combination therapy in melanoma patients with brain metastasis will be evaluated in study BRF117277, a phase II open label study of dabrafenib and trametinib in subjects with BRAF mutation positive melanoma that has metastasised to the brain.

The CHMP noted that in the two phase III studies only patients with BRAF V600 mutation tumours who were treatment naïve were included. The efficacy of combination therapy as second line therapy for patients who had been treated with BRAF inhibitors was not investigated. In the phase II study BRF113220, responses with the combination treatment were seen only in a limited percentage of patients (around 10%) who were previously treated with dabrafenib monotherapy. Response to the combination therapy was observed in patients who had achieved relative long-lasting (>6 months) response during treatment with dabrafenib monotherapy. Because of the lack of robust data in patients that have progressed on BRAF inhibitor therapy, a warning has been included in section 4.4 of the SmPC highlighting that there is limited data in this patient population and recommending prescribers to consider other treatment options before treatment with the combination in patients that have had prior treatment with BRAF inhibitors.

2.4.5. Conclusions on the clinical efficacy

The results of the two phase III studies for dabrafenib and trametinib combination therapy were generally consistent with each other and the results of the Phase II study BRF113220 part C were supportive. The benefits of dabrafenib and trametinib combination therapy in patients with advanced melanoma with BRAFV600 mutation were considered statistically significant and clinically relevant in terms of prolonged OS, PFS and increased response rates. The updated results from study MEK115306 and MEK116513 provided reassurance of the durability of the OS in the treated patient population.

2.5. Clinical safety

Introduction

Safety data include comparisons of combination dabrafenib+trametinib treatment to dabrafenib monotherapy in the Phase III Study MEK115306, and comparisons of combination dabrafenib+trametinib treatment to vemurafenib monotherapy in the Phase III Study MEK116513.

Data cut-off dates for the studies were as follows:

- MEK115306 (COMBI-d): 12 January 2015 (final overall survival [OS] analysis)
- MEK116513 (COMBI-v): 17 April 2014 (primary analysis)

The safety results of the phase II study BRF113220 Part C are considered as supportive to the results obtained in the phase III studies and have been described in the initial marketing application for Mekinist.

Patient exposure

Table 25: Exposure to dabrafenib and trametinib in Study MEK115306 (Safety Population)

	Trametinib or Placebo		Dabrafenib	
	Dabrafenib + Trametinib (N=209)	Dabrafenib + Placebo (N=211)	Dabrafenib + Trametinib (N=209)	Dabrafenib + Placebo (N=211)
Daily Dose (mg)				
n	209	211	209	211
Mean (SD)	1.9 (0.20)	1.9 (0.14)	273.6 (41.44)	284.8 (32.47)
Median (Min, Max)	2.0 (0.9, 2)	2.0 (1.2, 2)	294.7 (127.5, 300)	299.6 (118.6, 300)
Cumulative Dose (mg)				
n	209	211	209	211
Mean	866.1	679.0	125152.4	100840.9
(SD)	(582.95)	(539.08)	(86732.09)	(80640.47)
Median	688	496	99600	72900
(Min, Max)	(22, 1878)	(6, 1936)	(3300, 281100)	(900, 286200)
Time on Study Treatment (months)				
n	209	211	209	211
Mean (SD)	14.4 (9.82)	11.0 (9.10)	14.3 (9.81)	11.1 (9.07)
Median (Min, Max)	11.0 (0, 30)	8.0 (0, 32)	11.0 (0, 30)	8.0 (0, 32)
<3 months, n (%)	16 (8)	34 (16)	16 (8)	33 (16)
3-6 months, n (%)	43 (21)	57 (27)	43 (21)	57 (27)
>6-12 months, n (%)	54 (26)	48 (23)	54 (26)	49 (23)
>12 months, n (%)	96 (46)	72 (34)	96 (46)	72 (34)

Table 26: Exposure to trametinib, dabrafenib, and vemurafenib in Study MEK116513 (Safety Population)

	Dabrafenib + Trametinib (N=350)		Vemurafenib (N=349)
	Trametinib	Dabrafenib	
Daily Dose (mg)			
n	350	350	349
Mean (SD)	1.8 (0.27)	261.0 (52.58)	1615.9 (358.76)
Median (Min, Max)	2.0 (0.8, 2)	291.9 (112.4, 300)	1846.0 (450.4, 1920)
Cumulative Dose (mg)			
n	350	350	349
Mean (SD)	535.8 (279.68)	75867.7(41304.20)	354889.9(240452.07)
Median	554	75313	322560
(Min, Max)	(8, 1238)	(1200, 186000)	(2880, 1006080)
Time on Study Treatment (months)			
n	350	350	349
Mean (SD)	9.1 (4.80)	9.1 (4.84)	6.8 (4.63)
Median (Min, Max)	10.0 (0, 21)	10.0 (0, 21)	6.0 (0, 18)
<3 months, n (%)	33 (9)	32 (9)	81 (23)
3-6 months, n (%)	85 (24)	84 (24)	96 (28)
>6-12 months, n (%)	143 (41)	145 (41)	129 (37)
>12 months, n (%)	89 (25)	89 (25)	43 (12)

The median times on study treatment were similar for the combination arms in both studies, and longer than for the respective monotherapy arms. At the time of the data-cut-off almost half of the patients in MEK115306 and 25% of patients in the MEK116513 study had received more than 12 months of combination therapy.

Adverse events

Almost all patients in all treatment arms in both studies experienced an AE, and more than 85% of patients had an AE considered related to study treatment.

AEs leading to a dose modification (dose discontinuations, reductions or interruptions) were more common in the combination therapy arm compared with the dabrafenib monotherapy arm in MEK115306.

Table 27: Adverse event overview MEK115306 and MEK116513 (Safety Population)

	MEK115306		MEK116513	
	Dabrafenib + Trametinib N=209	Dabrafenib + Placebo N=211	Dabrafenib + Trametinib N=350	Vemurafenib N=349
Subjects With Any AE, n (%)	**203 (97)**	**205 (97)**	**343 (98)**	**345 (99)**
AEs related to study treatment	181 (87)	189 (90)	320 (91)	342 (98)
AEs leading to permanent discontinuation of study treatment	24 (11)	14 (7)	44 (13)	41 (12)
AE leading to dose reduction	59 (28)	29 (14)	115 (33)	136 (39)
AE leading to dose interruption	118 (56)	78 (37)	192 (55)	197 (56)
Subjects With Any SAE, n (%)	**88 (42)**	**78 (37)**	**131 (37)**	**122 (35)**
SAEs related to study treatment	62 (30)	52 (25)	92 (26)	90 (26)
Fatal SAEs	5 (2)	1 (<1)[a]	3 (<1)	3 (<1)
Fatal SAEs related to study treatment	0	1 (<1)[a]	0	0

a. A subject in the dabrafenib monotherapy arm MEK115306 had an SAE of bile duct adenocarcinoma that was considered by the investigator to be related to study treatment; this event was corrected to a fatal SAE post data cut-off

Table 28: Overview of adverse events in BRF113220 Part C, final CSR (cut-off 15 Jan 2014)

	Treatment Groups	
Dabrafenib	**150 mg BID**	**150 mg BID**
Trametinib	**--**	**2 mg QD**
N	**53**	**55**
Any AE, n (%)	**53 (100)**	**55 (100)**
AEs related to study treatment	51 (96)	55 (100)
AEs leading to permanent discontinuation of study treatment	1 (2)	8 (15)
AEs leading to dose reduction	13 (25)	33 (60)
AEs leading to dose interruption	18 (34)	40 (73)
Any SAE, n (%)	**14 (26)**	**38 (69)**
SAEs related to study treatment	10 (19)	25 (45)
Fatal SAEs	0	4 (7)
Fatal SAEs related to study treatment	0	0

AEs leading to permanent discontinuation of study treatment occurred in 11-13% of patients in the combination treatment, which was comparable to what was seen in the comparator arms of vemurafenib treatment (12%) but higher than for the dabrafenib arm, 7%.

AEs leading to dose reduction were reported for 28-33% of patients on the combination treatment, which was lower than for the comparator vemurafenib arm (39%) but higher than for the dabrafenib arm, 14%.

Any SAE was reported for 37-42% of patients on the combination arms, which was roughly similar to what was noted for both comparator arms (vemurafenib arm, 35% and dabrafenib arm, 37%).

Fatal SAEs were uncommon for all treatment arms (<1%-2% in the combination arms and <1% in patients on the comparator arms).

Table 29: Adverse events occurring in 10% or more subjects in any treatment arm in MEK115306 and MEK116513 (Safety Population)

	MEK115306		MEK116513	
Preferred Term	Dabrafenib +Trametinib N=209	Dabrafenib +Placebo N=211	Dabrafenib +Trametinib N=350	Vemurafenib N=349
Subjects with any event, n (%)	203 (97)	205 (97)	343 (98)	345 (99)
Pyrexia	119 (57)	69 (33)	184 (53)	73 (21)
Fatigue	81 (39)	79 (37)	101 (29)	115 (33)
Nausea	72 (34)	56 (27)	121 (35)	125 (36)
Headache	69 (33)	63 (30)	101 (29)	77 (22)
Chills	64 (31)	35 (17)	110 (31)	27 (8)
Diarrhea	63 (30)	33 (16)	112 (32)	131 (38)
Rash	56 (27)	46 (22)	76 (22)	149 (43)
Arthralgia	54 (26)	66 (31)	84 (24)	178 (51)
Vomiting	52 (25)	30 (14)	101 (29)	53 (15)
Hypertension	52 (25)	33 (16)	92 (26)	84 (24)
Oedema peripheral	44 (21)	19 (9)	42 (12)	35 (10)
Cough	44 (21)	44 (21)	69 (20)	34 (10)
Pain in extremity	32 (15)	36 (17)	33 (9)	41 (12)
Dizziness	29 (14)	14 (7)	34 (10)	21 (6)
Abdominal pain	28 (13)	18 (9)	30 (9)	28 (8)
Alanine aminotransferase increased	28 (13)	12 (6)	48 (14)	61 (17)
Aspartate aminotransferase increased	28 (13)	9 (4)	40 (11)	45 (13)
Constipation	27 (13)	22 (10)	48 (14)	61 (17)
Myalgia	27 (13)	28 (13)	58 (17)	51 (15)
Asthenia	26 (12)	30 (14)	55 (16)	57 (16)
Dry skin	26 (12)	34 (16)	29 (8)	62 (18)
Nasopharyngitis	26 (12)	21 (10)	40 (11)	27 (8)
Back pain	26 (12)	34 (16)	27 (8)	23 (7)
Decreased appetite	26 (12)	28 (13)	42 (12)	70 (20)
Pruritus	25 (12)	29 (14)	30 (9)	75 (21)
Urinary tract infection	22 (11)	7 (3)	20 (6)	6 (2)
Oropharyngeal pain	22 (11)	11 (5)	22 (6)	18 (5)
Abdominal pain upper	21 (10)	12 (6)	30 (9)	33 (9)
Dermatitis acneiform	20 (10)	8 (4)	22 (6)	20 (6)
Neutropenia	20 (10)	4 (2)	32 (9)	4 (1)
Alopecia	18 (9)	59 (28)	20 (6)	137 (39)
Hyperkeratosis	15 (7)	74 (35)	15 (4)	86 (25)
Dyspnoea	12 (6)	21 (10)	24 (7)	29 (8)
Palmar-plantar erythrodysaesthesia syndrome	11 (5)	39 (18)	8 (2)	55 (16)
Skin papilloma	4 (2)	46 (22)	6 (2)	80 (23)
Palmoplantar keratoderma	3 (1)	25 (12)	6 (2)	40 (11)
Muscle spasms	18 (9)	6 (3)	34 (10)	11 (3)
Erythema	18 (9)	16 (8)	30 (9)	40 (11)
Dysgeusia	6 (3)	13 (6)	23 (7)	46 (13)
Weight decreased	10 (5)	18 (9)	15 (4)	41 (12)
Blood creatinine increased	5 (2)	2 (<1)	14 (4)	37 (11)
Photosensitivity reaction	5 (2)	6 (3)	13 (4)	78 (22)
Conjunctivitis	5 (2)	4 (2)	9 (3)	34 (10)
Keratosis pilaris	2 (<1)	8 (4)	4 (1)	44 (13)
Squamous cell carcinoma	3 (1)	9 (4)	3 (<1)	34 (10)
Sunburn	2 (<1)	1 (<1)	2 (<1)	50 (14)

The most commonly reported AEs for the combination treatment were pyrexia, fatigue, nausea, diarrhoea, and chills, where the most commonly reported AEs in the comparator arm of dabrafenib were fatigue, hyperkeratosis, pyrexia, arthralgia, and headache and for vemurafenib arm, AEs were arthralgia, rash, alopecia, diarrhoea, nausea, and fatigue.

AEs that were more commonly reported in the combination arms in general vs the dabrafenib arm included pyrexia, nausea, chills, diarrhoea, vomiting, hypertension, oedema peripheral, dizziness, ALT increased, AST increased, urinary tract infection, neutropenia and muscle spasms and blood creatinine increased. In contrast, AEs that were less commonly reported were alopecia, palmar-plantar erythrodysaesthesia and terms related to hyperproliferative states of the skin.

AEs that were more commonly reported in the combination arms in general vs the vemurafenib arm included pyrexia, chills, vomiting, cough, neutropenia and muscle spasms. In contrast, the AEs that were less commonly reported were rash, decreased appetite, pruritus, alopecia, palmar-plantar erythrodysaesthesia, terms related to hyperproliferative states of the skin, dysgeusia, weight decreased, blood creatinine increased, photosensitivity reaction, conjunctivitis and sunburn.

Approximately half of the patients in the combination therapy arms in both studies had pyrexia that was considered related to study treatment which was 2 to 3 times higher incidence than either of the monotherapy arms. The next most common AEs (≥20%) considered related to study treatment in the combination arms of both studies were chills, fatigue, and nausea (Table 30).

Table 30: Adverse events related to study treatment occurring in 10% or more subjects in any treatment arm – Studies MEK115306 and MEK116513 (Safety population)

	MEK115306		MEK116513	
Preferred Term	**Dabrafenib + Trametinib (N=209)**	**Dabrafenib + Placebo (N=211)**	**Dabrafenib + Trametinib (N=350)**	**Vemurafenib (N=349)**
Subjects with any treatment-related event, n (%)	**181 (87)**	**189 (90)**	**320 (91)**	**342 (98)**
Pyrexia	108 (52)	52 (25)	163 (47)	54 (15)
Chills	58 (28)	29 (14)	98 (28)	21 (6)
Fatigue	56 (27)	59 (28)	70 (20)	92 (26)
Rash	50 (24)	42 (20)	68 (19)	146 (42)
Nausea	41 (20)	31 (15)	81 (23)	97 (28)
Headache	39 (19)	35 (17)	51 (15)	39 (11)
Diarrhea	38 (18)	19 (9)	71 (20)	104 (30)
Arthralgia	34 (16)	49 (23)	58 (17)	162 (46)
Vomiting	30 (14)	20 (9)	59 (17)	30 (9)
AST increased	22 (11)	6 (3)	32 (9)	37 (11)
Edema peripheral	22 (11)	4 (2)	24 (7)	20 (6)
ALT increased	20 (10)	7 (3)	35 (10)	49 (14)
Asthenia	19 (9)	19 (9)	43 (12)	43 (12)
Dry skin	19 (9)	29 (14)	21 (6)	59 (17)
Myalgia	18 (9)	17 (8)	46 (13)	46 (13)
Hypertension	17 (8)	14 (7)	45 (13)	31 (9)
Decreased appetite	16 (8)	14 (7)	23 (7)	55 (16)
Pruritus	15 (7)	23 (11)	22 (6)	67 (19)
Hyperkeratosis	13 (6)	70 (33)	12 (3)	79 (23)
Erythema	12 (6)	11 (5)	16 (5)	36 (10)
PPES	11 (5)	39 (18)	8 (2)	55 (16)
Alopecia	10 (5)	55 (26)	18 (5)	136 (39)
Dysgeusia	5 (2)	8 (4)	20 (6)	45 (13)
Photosensitivity reaction	3 (1)	5 (2)	12 (3)	78 (22)
Skin papilloma	3 (1)	39 (18)	6 (2)	76 (22)
Squamous cell carcinoma	3 (1)	9 (4)	3 (<1)	34 (10)
Keratosis pilaris	2 (<1)	7 (3)	2 (<1)	43 (12)
Palmoplantar keratoderma	2 (<1)	23 (11)	6 (2)	39 (11)
Sunburn	1 (<1)	0	2 (<1)	40 (11)

The most common AEs reported in the combination therapy group in study BRF113220 Part C were pyrexia, chills, fatigue, diarrhoea, nausea and vomiting, and the incidences of these AEs in the combination therapy group were higher than the incidences in the dabrafenib monotherapy group. Among the 5 most common AEs in the dabrafenib monotherapy group (fatigue, rash, arthralgia, alopecia and headache), the incidence of alopecia was higher (>10%) than the incidence in the combination therapy group.

The list of grade 3 and 4 events in the combination arms compared with dabrafenib or vemurafenib is presented in Table 31. Grade 3 events occurred in the combination therapy arms in 40% of the patients in study MEK115306 and approximately one-half of the patients in study MEK116513. Pyrexia and hypertension were the most common Grade 3 events in the combination therapy arms of both studies. Grade 4 events occurred in 5% of the patients in the combination therapy arms of both studies.

Table 31: Grade 3+4 adverse events occurring in 1% or more of subjects in any treatment arm in MEK115306 and MEK116513 (Safety Population)

	MEK115306						MEK116513					
	Dabrafenib + Trametinib N=209			Dabrafenib + Placebo N=211			Dabrafenib +Trametinib N=350			Vemurafenib N=349		
Preferred term												
Maximum Grade	3	4	Any	3	4	Any	3	4	Any	3	4	Any
Subjects with any event, n (%)	84 (40)	11 (5)	203 (97)	98 (46)	8 (4)	205 (97)	167 (48)	16 (5)	343 (98)	198 (57)	23 (7)	345 (99)
Pyrexia	15 (7)	0	119 (57)	4 (2)	0	69 (33)	15 (4)	0	184 (53)	2 (<1)	0	73 (21)
Fatigue	5 (2)	0	81 (39)	3 (1)	0	79 (37)	4 (1)	0	101 (29)	6 (2)	0	115 (33)
Nausea	1 (<1)	0	72 (34)	3 (1)	0	56 (27)	1 (<1)	0	121 (35)	2 (<1)	0	125 (36)
Headache	1 (<1)	0	69 (33)	3 (1)	0	63 (30)	3 (<1)	1 (<1)	101 (29)	2 (<1)	0	77 (22)
Diarrhea	3 (1)	0	63 (30)	2 (<1)	0	33 (16)	4 (1)	0	112 (32)	1 (<1)	0	131 (38)
Rash	0	0	56 (27)	2 (<1)	0	46 (22)	4 (1)	0	76 (22)	30 (9)	0	149 (43)
Arthralgia	2 (<1)	0	54 (26)	0	0	66 (31)	3 (<1)	0	84 (24)	15 (4)	0	178 (51)
Hypertension	12 (6)	0	52 (25)	13 (6)	0	33 (16)	48 (14)	0	92 (26)	32 (9)	1 (<1)	84 (24)
Vomiting	2 (<1)	0	52 (25)	1 (<1)	0	30 (14)	4 (1)	0	101 (29)	3 (<1)	0	53 (15)
Pain in extremity	3 (1)	0	32 (15)	2 (<1)	0	36 (17)	4 (1)	0	33 (9)	1 (<1)	0	41 (12)
Abdominal pain	2 (<1)	0	28 (13)	5 (2)	0	18 (9)	1 (<1)	0	30 (9)	3 (<1)	0	28 (8)
Alanine aminotransferase increased	5 (2)	0	28 (13)	0	1 (<1)	12 (6)	9 (3)	0	48 (14)	13 (4)	2 (<1)	61 (17)
Aspartate aminotransferase increased	7 (3)	0	28 (13)	1 (<1)	1 (<1)	9 (4)	4 (1)	1 (<1)	40 (11)	9 (3)	0	45 (13)
Myalgia	1 (<1)	0	27 (13)	0	0	28 (13)	0	0	58 (17)	4 (1)	0	51 (15)
Asthenia	3 (1)	0	26 (12)	2 (<1)	0	30 (14)	4 (1)	1 (<1)	55 (16)	4 (1)	0	57 (16)
Back pain	2 (<1)	0	26 (12)	5 (2)	0	34 (16)	0	0	27 (8)	2 (<1)	0	23 (7)
Urinary tract infection	4 (2)	0	22 (11)	1 (<1)	0	7 (3)	3 (<1)	0	20 (6)	0	0	6 (2)
Dermatitis acneiform	0	0	20 (10)	0	0	8 (4)	0	0	22 (6)	4 (1)	0	20 (6)
Neutropenia	7 (3)	0	20 (10)	1 (<1)	0	4 (2)	17 (5)	0	32 (9)	2 (<1)	1 (<1)	4 (1)
Blood alkaline phosphatase increased	1 (<1)	0	17 (8)	0	0	8 (4)	7 (2)	0	25 (7)	5 (1)	0	29 (8)
Influenza like illness	1 (<1)	0	17 (8)	0	0	11 (5)	4 (1)	0	30 (9)	0	0	14 (4)
Anemia	5 (2)	1 (<1)	13 (6)	9 (4)	0	20 (9)	6 (2)	0	26 (7)	4 (1)	0	17 (5)
Dyspnea	1 (<1)	0	12 (6)	3 (1)	1 (<1)	21 (10)	3 (<1)	0	24 (7)	2 (<1)	1 (<1)	29 (8)
Ejection fraction decreased	3 (1)	0	12 (6)	4 (2)	0	7 (3)	13 (4)	0	29 (8)	0	0	0
Hypotension	4 (2)	0	12 (6)	1 (<1)	0	7 (3)	3 (<1)	0	15 (4)	0	0	1 (<1)
Rash maculo-papular	0	0	12 (6)	1 (<1)	0	8 (4)	2 (<1)	0	13 (4)	13 (4)	0	28 (8)
Actinic keratosis	0	0	10 (5)	3 (1)	0	15 (7)	0	0	5 (1)	2 (<1)	0	25 (7)
Syncope	5 (2)	0	10 (5)	1 (<1)	0	2 (<1)	5 (1)	0	12 (3)	0	0	1 (<1)
Pneumonia	3 (1)	0	9 (4)	1 (<1)	0	4 (2)	0	0	2 (<1)	2 (<1)	0	4 (1)
Hyperglycemia	4 (2)	1 (<1)	8 (4)	0	0	3 (1)	6 (2)	2 (<1)	17 (5)	4 (1)	1 (<1)	11 (3)
Hypophosphatemia	2 (<1)	0	8 (4)	4 (2)	0	6 (3)	5 (1)	0	10 (3)	1 (<1)	0	4 (1)
Leukopenia	1 (<1)	0	8 (4)	0	0	1 (<1)	4 (1)	0	14 (4)	2 (<1)	0	6 (2)
Basal cell carcinoma	6 (3)	0	7 (3)	13 (6)	0	13 (6)	2 (<1)	0	3 (<1)	3 (<1)	0	3 (<1)
C-reactive protein increased	4 (2)	0	7 (3)	1 (<1)	0	2 (<1)	0	0	8 (2)	0	0	2 (<1)
Hypokalemia	2 (<1)	0	7 (3)	1 (<1)	1 (<1)	4 (2)	3 (<1)	0	13 (4)	4 (1)	0	15 (4)
Blood creatine phosphokinase increased	0	0	6 (3)	0	0	0	2 (<1)	3 (<1)	7 (2)	0	1 (<1)	1 (<1)
Gamma-glutamyltransferase increased	3 (1)	0	5 (2)	2 (<1)	0	5 (2)	15 (4)	0	31 (9)	14 (4)	3 (<1)	33 (9)
General physical health deterioration	3 (1)	0	5 (2)	2 (<1)	0	3 (1)	1 (<1)	0	2 (<1)	1 (<1)	1 (<1)	3 (<1)
Pulmonary embolism	2 (<1)	1 (<1)	5 (2)	1 (<1)	0	1 (<1)	7 (2)	0	7 (2)	2 (<1)	0	2 (<1)
Hyponatremia	3 (1)	0	4 (2)	2 (<1)	0	2 (<1)	14 (4)	1 (<1)	16 (5)	8 (2)	0	12 (3)
Lymphocyte count decreased	3 (1)	1 (<1)	4 (2)	4 (2)	0	5 (2)	4 (1)	0	8 (2)	3 (<1)	0	7 (2)
Lymphopenia	1 (<1)	0	4 (2)	3 (1)	0	4 (2)	3 (<1)	0	6 (2)	4 (1)	0	8 (2)
Squamous cell carcinoma	3 (1)	0	3 (1)	9 (4)	0	9 (4)	3 (<1)	0	3 (<1)	32 (9)	1 (<1)	34 (10)
Dehydration	1 (<1)	0	3 (1)	1 (<1)	0	4 (2)	6 (2)	0	15 (4)	2 (<1)	0	6 (2)
Hepatic enzyme increased	1 (<1)	0	3 (1)	0	0	3 (1)	4 (1)	1 (<1)	9 (3)	3 (<1)	2 (<1)	8 (2)

Preferred term	MEK115306						MEK116513					
	Dabrafenib + Trametinib N=209			Dabrafenib + Placebo N=211			Dabrafenib +Trametinib N=350			Vemurafenib N=349		
Maximum Grade	3	4	Any	3	4	Any	3	4	Any	3	4	Any
Subjects with any event, n (%)	84 (40)	11 (5)	203 (97)	98 (46)	8 (4)	205 (97)	167 (48)	16 (5)	343 (98)	198 (57)	23 (7)	345 (99)
Squamous cell carcinoma of skin	2 (<1)	0	2 (<1)	11 (5)	0	11 (5)	1 (<1)	0	1 (<1)	16 (5)	1 (<1)	17 (5)
Rash generalized	0	0	2 (<1)	0	0	1 (<1)	0	0	1 (<1)	4 (1)	0	9 (3)
Keratoacanthoma	1 (<1)	0	1 (<1)	4 (2)	0	4 (2)	1 (<1)	0	1 (<1)	32 (9)	1 (<1)	33 (9)
Electrocardiogram QT prolonged	0	0	0	2 (<1)	0	5 (2)	1 (<1)	1 (<1)	5 (1)	5 (1)	1 (<1)	12 (3)

Grade 4 events were reported for 5%, 4% and 7% of patients treated with the combination treatment in both studies, dabrafenib and vemurafenib arm respectively. Thus, grade 4 events were slightly more commonly reported for vemurafenib than for the other treatments and dominated by hepatic laboratory events.

Grade 3 events were reported for 40-48% of subjects in the combination arms, 46% in the dabrafenib arm, and 57% in the vemurafenib arm. The preferred terms (PTs) reported in ⩾5% of subjects in at least 1 study arm were pyrexia (4-7%), hypertension (6-14%) and neutropenia (3-5%) for the combination treatment compared to hypertension (6%), basal cell carcinoma (6%) and squamous cell carcinoma of skin (5%) for the dabrafenib monotherapy arm, and rash (9%), hypertension (9%), squamous cell carcinoma (9%), squamous cell carcinoma of skin (5%) and keratoacanthoma (9%) for the vemurafenib arm. Thus, grade 3 events were more commonly reported for patients treated with vemurafenib. Monotherapy with either dabrafenib or vemurafenib was associated with more events related to hyperproliferative states of the skin than combined BRAF and MEK inhibition therapy.

In the combination therapy group in study BRF113220 Part C, neutropenia was the most frequently reported Grade ≥3 AE. In the dabrafenib monotherapy group, the most frequently reported Grade ≥3 AEs were SCC (cutaneous) and fatigue.

Table 32 summarises the adverse events for which it was considered that there is sufficient evidence to suggest a causal relationship with the administration of trametinib in combination with dabrafenib.

Table 32: Adverse reactions occurring in patients treated with trametinib and dabrafenib in study MEK115306 (n=209)[e]

System Organ Class	Adverse Reactions	Frequency (%)
Infections and Infestations	Urinary tract infection	11
	Nasopharyngitis	12
	Cellulitis	3
	Folliculitis	6
	Paronychia	2
	Rash pustular	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Cutaneous squamous cell carcinoma[b]	3
	Papilloma[c]	2
	Seborrhoeic keratosis	4
	Acrochordon (skin tags)	1
	New primary melanoma	<1
Blood and lymphatic system disorders	Neutropenia	10
	Anaemia	6
	Thrombocytopenia	4

	Leukopenia	4
Immune system disorders	Drug Hypersensitivity	<1
Metabolism and nutrition disorders	Decreased appetite	12
	Dehydration	1
	Hyponatraemia	2
	Hypophosphataemia	4
	Hyperglycaemia	4
Nervous system disorders	Headache	33
	Dizziness	14
Eye disorders	Vision blurred	3
	Visual impairment	2
	Chorioretinopathy	<1
	Uveitis	<1
	Retinal detachment	<1
	Periorbital oedema	<1
Cardiac disorder	Ejection fraction decreased	6
Vascular disorders	Hypertension	25
	Haemorrhage[d]	19
	Hypotension	6
	Lymphoedema	<1
Respiratory, thoracic and mediastinal disorders	Cough	21
	Dyspnoea	6
	Pneumonitis	<1
Gastrointestinal disorders	Abdominal pain	13
	Constipation	13
	Diarrhoea	30
	Nausea	34
	Vomiting	25
	Dry mouth	8
	Stomatitis	1
	Pancreatitis	<1
Hepatobiliary disorder	Alanine aminotransferase increased	13
	Aspartate aminotransferase increased	13
	Blood alkaline phosphatase increased	8
	Gamma-glutamyltransferase increased	2
Skin and subcutaneous disorders	Dry skin	12
	Pruritus	12
	Rash	27
	Dermatitis acneiform	10
	Erythema	9
	Actinic keratosis	5
	Night sweats	6
	Hyperkeratosis	7
	Alopecia	9
	Palmar-plantar erythrodysaesthesia syndrome	5
	Skin lesion	3
	Hyperhidrosis	7

	Panniculitis	2
	Skin Fissures	2
Musculoskeletal and connective tissue disorders	Arthralgia	26
	Myalgia	13
	Pain in extremity	15
	Muscle spasms	9
	Blood creatine phosphokinase increased	3
Renal and urinary disorders	Renal failure[a]	<1
	Nephritis	<1
General disorders and administration site conditions	Fatigue	39
	Chills	31
	Asthenia	12
	Oedema peripheral	21
	Pyrexia	57
	Mucosal inflammation	2
	Influenza-like illness	8
	Face oedema	2

[a] Renal failure, renal failure acute
[b] cu SCC: SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma
[c] Papilloma, skin papilloma
[d] Bleeding from various sites, including intracranial bleeding and fatal bleeding
[e]Additional adverse reactions which occurred with frequencies <1% in other studies with trametinib in combination with dabrafenib were rhabdomyolysis, interstitial lung disease, cardiac failure and left ventricular dysfunction

Serious adverse event / deaths / other significant events

SAEs including protocol specified events occurred in approximately 40% of patients in the combination therapy arms of both studies. The incidence of SAEs (35-42%) and SAEs considered related to the investigational product by the investigator (25-30%) were similar across all 4 treatment arms for both studies.

Pyrexia was the most common SAE in the combination therapy arms, followed by ejection fraction decreased and chills for both studies.

Table 33: Serious adverse events occurring in 1% or more subjects in any treatment arm in MEK115306 and MEK116513 (Safety Population)

	MEK115306		MEK116513	
Preferred Term	Dabrafenib + Trametinib N=209	Dabrafenib + Placebo N=211	Dabrafenib + Trametinib N=350	Vemurafenib N=349
Subjects with Any Serious Event, n (%)	88 (42)	78 (37)	131 (37)	122 (35)
Pyrexia	35 (17)	15 (7)	49 (14)	6 (2)
Chills	9 (4)	3(1)	13 (4)	0
Ejection fraction decreased	9 (4)	5 (2)	24 (7)	0
Basal cell carcinoma	7 (3)	13 (6)	3 (<1)	3 (<1)
Hypotension	6 (3)	2 (<1)	5 (1)	0
Pneumonia	6 (3)	2 (<1)	0	4 (1)
Abdominal pain	3 (1)	2 (<1)	0	1 (<1)
ALT increased	3 (1)	0	5 (1)	8 (2)
Confusional state	3 (1)	1 (<1)	0	1 (<1)
Fatigue	3 (1)	1 (<1)	2 (<1)	1 (<1)
Pulmonary embolism	3 (1)	1 (<1)	4 (1)	0
Squamous cell carcinoma[a]	3 (1)	9 (4)	3 (<1)	33 (9)
Syncope	3 (1)	1 (<1)	1 (<1)	0
Vomiting	3 (1)	0	7 (2)	1 (<1)
Anemia	2 (<1)	3 (1)	3 (<1)	2 (<1)
Atrial fibrillation	2 (<1)	2 (<1)	2 (<1)	4 (1)
Nausea	2 (<1)	0	4 (1)	1 (<1)
Squamous cell carcinoma of skin[a]	2 (<1)	11 (5)	1 (<1)	17 (5)
AST increased	1 (<1)	0	3 (<1)	5 (1)
Dehydration	1 (<1)	2 (<1)	8 (2)	2 (<1)
Hepatic enzyme increased	1 (<1)	0	4 (1)	6 (2)
Malignant melanoma	1 (<1)	2 (<1)	1 (<1)	4 (1)
Urinary tract infection	1 (<1)	1 (<1)	6 (2)	1 (<1)
Blood bilirubin increased	0	0	1 (<1)	6 (2)
Erysipelas	0	0	4 (1)	0
Hyponatremia	0	1 (<1)	5 (1)	0
Keratoacanthoma	0	1 (<1)	1 (<1)	21 (6)
Pericarditis	0	0	0	4 (1)
Renal failure	0	0	4 (1)	0

a. Events were reported under either preferred term, both denote squamous cell cancer occurring in the skin

Deaths

Fewer patients died in the combination therapy arm compared with the respective monotherapy arm in both studies. The primary cause of death in all treatment arms was disease under study, and most of the deaths occurred more than 30 days after the last dose of study treatment.

No patients in the combination therapy or vemurafenib arms had fatal SAEs that were considered related to study treatment by the investigator, the 1 fatal SAE in the dabrafenib arm was considered related by the investigator.

Table 34: Fatal adverse events in MEK115306 and MEK116513 (Safety Population)

Preferred Term	MEK115306		MEK116513	
	Dabrafenib + Trametinib (N=209)	Dabrafenib + Placebo (N=211)	Dabrafenib + Trametinib (N=350)	Vemurafenib (N=349)
Any Event, n (%)	5 (2)	1 (<1)	3 (<1)	3 (<1)
Cerebral hemorrhage	2 (<1)	0	2 (<1)	0
Cerebrovascular accident[a]	1 (<1)	0	0	0
Myocardial ischemia[b]	1 (<1)	0	0	0
Pneumonia	1 (<1)	0	0	0
Acute coronary syndrome	0	0	0	1 (<1)
Bile duct adenocarcinoma[c]	0	1 (<1)	0	0
Brain stem hemorrhage	0	0	1 (<1)	0
Cerebral ischemia	0	0	0	1 (<1)
Pleural infection	0	0	0	1 (<1)

a. A subject in Study MEK115306 was initially reported as having a cerebrovascular accident, which was identified as cerebral haemorrhage as the admission CT scan and on later autopsy
b. this event has been updated to "unknown" post data cut-off
c. a subject in the dabrafenib monotherapy arm of MEK115306 had an SAE of bile duct adenocarcinoma that was considered by the investigator to be related to study treatment; this event was corrected to a fatal SAE post data cut-off

In study BRF113220 Part C, four fatal SAEs were reported for the combination therapy arm (vs 0 in the dabrafenib monotherapy arm): 2 patients with intracranial haemorrhage (in 1 patient with grade 4 thrombocytopenia and 1 patient likely on post pulmonary embolism treatment), 1 with cerebrovascular accident, and 1 with pulmonary embolism.

Adverse Events of Special Interest

Adverse events of special interest and additional events of interest include events that are either known class effects, were identified pre-clinically or in prior clinical studies, or are potentially life threatening. The AEs of special interest are presented in Table 35.

Adverse events of special interest and additional events of interest in both treatment arms in MEK115306 and MEK116513 were primarily Grades 1 and 2 with the exception of malignancies and PE/DVT.

The AEs of special interest and additional events of interest with the highest incidence of Grade 3 events (defined as ≥5% difference to the monotherapy arm) in the combination arm of either or both studies were hypertension, pyrexia, hepatic events and neutropenia. In study MEK115306, the incidence of Grade 3 events for pyrexia and hepatic events were higher (≥5% difference) in the combination arm than in the dabrafenib monotherapy arm. In study MEK116513, pyrexia, hypertension and neutropenia were reported more frequently in the combination arm than in the vemurafenib monotherapy arm.

Table 35: Adverse events of special interest in MEK115306 and MEK116513 (Safety Population)

AEs of Special Interest Category	MEK115306		MEK116513	
	Dabrafenib + Trametinib (N=209)	Dabrafenib + Placebo (N=211)	Dabrafenib + Trametinib (N=350)	Vemurafenib (N=349)
Subjects with event, n (%)				
Key Events of Interest				
Pyrexia	129 (62)	79 (37)	200 (57)	89 (26)
Skin-related toxicities	101 (48)	112 (53)	157 (45)	267 (77)
Diarrhea	63 (30)	33 (16)	112 (32)	131 (38)
Hypertension	54 (26)	36 (17)	94 (27)	90 (26)
Bleeding events	40 (19)	32 (15)	62 (18)	25 (7)
Hepatic events	39 (19)	25 (12)	92 (26)	110 (32)
Ocular events	27 (13)	23 (11)	39 (11)	47 (13)
Cardiac-related events	12 (6)	10 (5)	29 (8)	1 (<1)
Treatment-Emergent Malignancies				
CuSCC[a]	6 (3)	22 (10)	5 (1)	63 (18)
New primary melanoma	1 (<1)	4 (2)	2 (<1)	7 (2)
Other treatment-emergent malignancies	3 (1)	7 (3)[b]	3 (<1)	2 (<1)[c]
Pneumonitis	2 (<1)	0	4 (1)	1 (<1)
Additional Events of Interest				
Edema	53 (25)	23 (11)	63 (18)	44 (13)
Hypersensitivity	35 (17)	14 (7)	36 (10)	44 (13)
Neutropenia	30 (14)	9 (4)	50 (14)	10 (3)
Hyperglycemia	15 (7)	7 (3)	23 (7)	17 (5)
Renal insufficiency	8 (4)	5 (2)	24 (7)	42 (12)
Deep vein thrombosis and pulmonary embolism	6 (3)	2 (<1)	8 (2)	2 (<1)
Pancreatitis	1 (<1)	1 (<1)	2 (<1)	3 (<1)

a. includes events that were reported under the preferred terms
b. includes a subject who was mistakenly reported with 2 events of other treatment-emergent malignancies
c. includes a subject who upon subsequent clinical review was identified as having carcinoma in situ of skin

Pyrexia was the most common AE reported for the combination treatment. Median time to onset for the first occurrence was 29-38 days with a median duration of 3 days; the event occurred at ⩾3 events in 22-33% of subjects on the combination arm vs 2-7% of the monotherapy BRAF inhibitor arms. No grade 4 event was reported but 11-14% of patients on the combination were hospitalised due to pyrexia, compared to 5% for dabrafenib monotherapy and 1% for vemurafenib.

Median time to onset for the first occurrence of **cutaneous squamous cell carcinoma** was 139-223 days with combination treatment vs 60-63 days with the monotherapy BRAF inhibitor arms. The incidence of Grade 3 events was higher (≥5% difference) for cuSCC in the dabrafenib arm compared with the combination therapy arm in MEK115306. In MEK116513 the incidences of Grade 3 events were higher (≥5% difference) for cuSCC and skin-related toxicities in the vemurafenib arm compared with the combination therapy arm.

New primary melanoma was reported in 2% of patients in the monotherapy arms vs ⩽1% in the combination population.

Other treatment-emergent malignancies were reported in 3% of patients on the monotherapy dabrafenib arm vs ⩽1-1% of patients on the other arms with median time to onset of 239-330 days for the combination, 160 days for dabrafenib monotherapy and 88 days for vemurafenib. In total, 1 patient on combination treatment was discontinued from therapy due to the event.

Bleeding events were more commonly reported on dabrafenib-containing regimens; combination 18-19%, monotherapy dabrafenib 15% and 7% for vemurafenib with epistaxis grade <3 being the

predominant PT for all dabrafenib-containing arms. Grade 3 events were reported for 1-2% of patients on combination treatment. Median time to onset of 1st event was 94 days for the combination. Of note, 3 fatal events were reported for the combination in each of the MEK115306 and MEK116513 studies, all intracranial haemorrhage, vs none in the monotherapy treatment arms. For 5 of the 6 fatal cases of intracranial haemorrhage there were confounding factors including the use of anticoagulant therapy (2 subjects), presence of brain metastases (2 subjects), and cerebral haemorrhage after a fall in a setting of grade 3 thrombocytopenia (1 subject).

Cardiac-related events, all due to EF decreased or LV dysfunction/cardiac failure, were more common in the dabrafenib-containing treatment arms (5-8%) than in the vemurafenib arm (<1%) but no grade 4 event occurred. Median time to first occurrence was 88-157 days for the combination and 123 days for dabrafenib monotherapy with a duration of first occurrence of 24-27 days and 43 days, respectively. One or both study treatments were withdrawn due to cardiac-related events for ⩽3% of subjects in the combination therapy arms and for <1% in the dabrafenib arm. Regarding EF, higher fractions of patients on the combination than on dabrafenib monotherapy met dose interruption criteria (EF decrease >10% from baseline and below the institutional LLN), 5-7% vs 2%.

Hypertension was more common on combination treatment (26-27%) and vemurafenib (26) than on dabrafenib (17%) with grade 3 events occurring in 6-14% of patients on combination treatment; no grade 4 event was reported for dabrafenib-containing therapy. Median time to onset of first occurrence was 56-58 days for the combination, with a median duration of 27-29 days; ⩾3 occurrences were reported for 3% of patients; no treatment discontinuation due to the event was reported for the combination therapy arms or the dabrafenib monotherapy arm.

Ocular events were reported at similar frequencies for all study arms, 11-13%, with grade 3 events occurring in up to 1% in the combination and vemurafenib arms; no grade 4 events were reported; discontinuation of study treatment was reported for <1% of patients.

Six patients (1%), whereof 1 grade 3, in the combination therapy arms, 1 patient (<1%) in the vemurafenib arm, and no patients in the dabrafenib arm had **pneumonitis** events reported.

Skin-related toxicities, mainly rash, were more common in the vemurafenib arm (77%; grade 3 in 16%) than in the combination arms (45-48%; grade 3 in <1-2%) and the dabrafenib monotherapy arm (53%; grade 3 in 2%). Study treatment discontinuation due to the event was noted in the vemurafenib arm, 1%.

Diarrhoea was more common in the vemurafenib arm (38%) and the trametinib-containing study arms (30-32%) than in the dabrafenib monotherapy arm (16%). With combination treatment, the median duration of the first event was 3 days and ⩾3 events were recorded in 3-5% of these patients; dose reduction was reported for up to 1% of patients.

Regarding **hepatic events**, GGT was not routinely collected in the MEK115306 study, most likely contributing to the higher incidence of hepatic events noted in the MEK116513 study. Grade 3 events were reported for 7-9% of patients on combination treatment, 1% of patients on dabrafenib monotherapy, and 10% of patients on the vemurafenib arm; the corresponding figures for grade 4 events were 0-<1%, <1% and 2%. Study treatment was discontinued due to the event in up to 2% of patients on combination treatment, and dose reduction noted in up to 4% of patients. None of the 6 patients with concurrent specified increases of ALT and bilirubin on combination treatment fulfilled Hy' s law vs 3/12 in the vemurafenib arm. Out of 10 patients on combination treatment that developed ALT ⩾8x ULN (stopping criterion) 3 were negatively re-challenged.

No patient on combination treatment discontinued treatment due to **hypersensitivity**.

Oedema was more common with combination treatment (18-25%; grade 3 <1-1%; median time to 1st occurrence 113-130 days, median duration of 1st occurrence 29-37 days) than with dabrafenib monotherapy (11%) or vemurafenib (13%). Discontinuation due to the event and dose reduction were reported in <1% of patients on combination treatment.

Neutropenia was more common with combination treatment (14%; grade 3 in 4-7%; grade 4 in <1%; median time to 1st occurrence 50-153 days, median duration of 1st occurrence 19-27 days) than with dabrafenib monotherapy (4%) or vemurafenib (3%). Treatment discontinuation due to the event was reported for 1 patient on combination therapy, dose reduction for up to3% and dose interruption for up to 7%.

Pancreatitis was reported for 3 patients (<1%) on combination treatment whereof 1 of grade 4; no dose adjustments were required.

PE and DVT were reported in 2-3% of patients on combination treatment (grade 3 in 1-2%; grade 4 in 1 patient; median time to 1st occurrence 169-280 days, median duration of 1st occurrence 29-31 days), higher than noted for the monotherapy arms (<1%). While dose interruption due to the event was reported for 3 patients on combination treatment, no patient had the dose reduced or discontinued study treatment.

Renal insufficiency was reported in 4-7% of patients on combination treatment (grade 3 in <1-1%; grade 4 in 1 patient; median time to 1st occurrence 108-147 days, median duration of 1st occurrence 4-16 days) and 2% for patients on the dabrafenib arm, lower than noted for the vemurafenib arm (12%). Four patients on combination therapy discontinued treatment due to the event.

For the combination therapy, AE of **QTc prolongation** was reported in no patient in the MEK115306 study and in 5 patients in the MEK116513 study, whereof 4 with an increase to ≥ 501 msec including 2 that also had an increase >60 msec from baseline that subsequently resolved. QTc prolongation was reported for 5 patients in the dabrafenib monotherapy arm and 12 patients in the vemurafenib arm.

Laboratory findings

Clinical chemistry assessments

In MEK115306, a higher percentage of subjects in the combination therapy arm had "any grade" increases in hypoalbuminemia (53%, with 1% grade 3, vs 27%), hypokalemia (13%, with 2% grade 3, vs 10%) and hyponatremia (24%, with 6% grade 3, vs 14%) than in the dabrafenib monotherapy arm. For the combination arm 1 grade 4 event was reported, hyperglycaemia.

In MEK116513, a higher percentage of subjects in the combination therapy arm had "any grade" changes from baseline in hypoalbuminemia (45%, with <1% grade 3, vs 15%) and hypophosphatemia (39%, with 7% grade 3 and 1 grade 4 event, vs 23%) than in the vemurafenib monotherapy arm, and a lower percentage of subjects had "any grade" change from baseline in creatinine in the combination therapy arm compared with vemurafenib monotherapy (12% vs 35%). For the combination arm 6 grade 4 events were reported; creatinine increase (n=1), hyperglycaemia (3), hyponatremia (1), and hypophosphatemia (1).

Haematology assessments

In MEK115306, the percentage of patients with increases of any grade and to Grade 3 neutropenia from baseline was higher in the combination therapy arm than in the dabrafenib monotherapy arm. The percentage of patients with increases to Grade 3 or Grade 4 in haemoglobin, lymphocyte count decreased, platelets, and leukocytes from baseline were similar between the treatment arms.

In MEK116513, the percentage of patients with change from baseline of any grade and to Grade 3

neutropenia and leukopenia from baseline was higher in the combination therapy arm than in the vemurafenib monotherapy arm. The percentages of patients with changes from baseline to Grade 3 or Grade 4 in haemoglobin, lymphocyte count decrease, and platelets decrease from baseline were similar between the treatment arms, although the combination therapy arm showed a higher incidence of "any grade" increase for platelet counts.

Safety in special populations

Age

The adverse events overview for patients <65 years and ≥65 years are presented in Table 36.

Table 36: Adverse events overview by age (<65 vs ≥65)

Age <65	MEK115306		MEK116513	
	Dabrafenib +Trametinib (N=153)	Dabrafenib +Placebo (N=151)	Dabrafenib +Trametinib (N=273)	Vemurafenib (N=262)
Subjects with any AE, n (%)	**147 (96)**	**145 (96)**	**267 (98)**	**259 (99)**
AEs related to study treatment	130 (85)	133 (88)	246 (90)	256 (98)
AEs leading to permanent discontinuation of study treatment	15 (10)	8 (5)	23 (8)	28 (11)
AE leading to dose reduction	35 (23)	17 (11)	78 (29)	90 (34)
AE leading to dose interruption	81 (53)	49 (32)	139 (51)	140 (53)
Subjects with any SAE, n (%)	**55 (36)**	**48 (32)**	**92 (34)**	**75 (29)**
SAEs related to study treatment	37 (24)	31 (21)	63 (23)	50 (19)
Fatal SAEs	3 (2)	0	1 (<1)	2 (<1)
Fatal SAEs related to study treatment	0	0	0	0
Age ≥65	**Dabrafenib +Trametinib (N=56)**	**Dabrafenib +Placebo (N=60)**	**Dabrafenib +Trametinib (N=77)**	**Vemurafenib (N=87)**
Subjects with any AE, n (%)	**56 (100)**	**60 (100)**	**76 (99)**	**86 (99)**
AEs related to study treatment	51 (91)	56 (93)	74 (96)	86 (99)
AEs leading to permanent discontinuation of study treatment	9 (16)	6 (10)	21 (27)	13 (15)
AE leading to dose reduction	24 (43)	12 (20)	37 (48)	46 (53)
AE leading to dose interruption	37 (66)	29 (48)	53 (69)	57 (66)
Subjects with any SAE, n (%)	**33 (59)**	**30 (50)**	**39 (51)**	**47 (54)**
SAEs related to study treatment	25 (45)	21 (35)	29 (38)	40 (46)
Fatal SAEs	2 (4)	1 (<1)[a]	2 (3)	1 (1)
Fatal SAEs related to study treatment	0	1 (<1)[a]	0	0

Gender

The incidence of the most common AEs in the combination therapy arms were generally similar between male and female patients, with the exception of nausea, vomiting, rash, arthralgia, and cough which were more common (≥5% difference) in female patients compared with male patients for both studies, and hypertension, which was more common (≥5% difference) in male patients compared with female patients for both studies.

Safety related to drug-drug interactions and other interactions

The MAH did not submit studies related to drug-drug interactions (see safety discussion).

Administration of dabrafenib and trametinib in combination had no clinically relevant effect on the exposure of trametinib or of dabrafenib monotherapy (see pharmacology section).

Discontinuation due to adverse events

The incidence of AEs leading to permanent discontinuation of study treatment was higher in the combination therapy arm compared with the dabrafenib arm for MEK115306 of study. The proportions were similar for the treatment arms in MEK116513.

AEs leading to discontinuation in ≥1% of the patients were pyrexia and ejection fraction decrease in the combination therapy arms, ejection fraction decrease in the dabrafenib arm, and arthraligia, ALT increased, and aspartate aminotransferease (AST) increased in the vemurafenib arm.

Table 37: Adverse events leading to permanent discontinuation of study treatment in 1% or more subjects in any treatment arm in MEK115306 and MEK116513 (Safety Population)

Preferred Term	MEK115306		MEK116513	
	Dabrafenib + Trametinib N=209	Dabrafenib + Placebo N=211	Dabrafenib + Trametinib N=350	Vemurafenib N=349
Subjects with Any Event, n (%)	24 (11)	14 (7)	44 (13)	41 (12)
Pyrexia	5 (2)	2 (<1)	12 (3)	1 (<1)
Ejection fraction decreased	3 (1)	3 (1)	10 (3)	0
ALT increased	2 (<1)	0	3 (<1)	4 (1)
Arthralgia	1 (<1)	0	0	7 (2)
AST increased	1 (<1)	0	2 (<1)	5 (1)

Adverse Events Leading to Interruption and Dose Reduction of Study Treatment

The most common AE leading to dose reduction was pyrexia in the combination therapy and dabrafenib arms, and rash and arthralgia in the vemurafenib arm.

Table 38: Adverse events leading to dose reduction in 3% or more subjects in any treatment arm in MEK115306 and MEK116513 (Safety Population)

Preferred Term	MEK115306		MEK116513	
	Dabrafenib + Trametinib N=209	Dabrafenib + Placebo N=211	Dabrafenib + Trametinib N=350	Vemurafenib N=349
Subjects with Any Event, n (%)	59 (28)	29 (14)	115 (33)	136 (39)
Pyrexia	29 (14)	6 (3)	49 (14)	10 (3)
Ejection fraction decreased	4 (2)	1 (<1)	13 (4)	0
Rash	4 (2)	2 (<1)	5 (1)	37 (11)
ALT increased	3 (1)	0	2 (<1)	11 (3)
Fatigue	3 (1)	3 (1)	1 (<1)	9 (3)
Arthralgia	1 (<1)	0	4 (1)	17 (5)
Rash maculo-papular	0	2 (<1)	2 (<1)	10 (3)

The most commons AEs leading to dose interruption in the combination arms and the dabrafenib monotherapy arm were pyrexia and chills. Rash, arthralgia, and increased ALT, were the most common AEs leading to dose interruption in the vemurafenib arm.

Table 39: Adverse events leading to dose interruption in 3% or more subjects in any treatment arm in MEK115306 and MEK116513 (Safety Population)

	MEK115306		MEK116513	
Preferred Term	Dabrafenib + Trametinib N=209	Dabrafenib + placebo N=211	Dabrafenib + Trametinib N=350	Vemurafenib N=349
Subjects with Any Event, n (%)	118 (56)	78 (37)	192 (55)	197 (56)
Pyrexia	73 (35)	29 (14)	106 (30)	14 (4)
Chills	22 (11)	8 (4)	27 (8)	2 (<1)
Vomiting	15 (7)	3 (1)	15 (4)	6 (2)
Nausea	11 (5)	4 (2)	18 (5)	14 (4)
Ejection fraction decreased	10 (5)	4 (2)	20 (6)	0
Diarrhea	9 (4)	2 (<1)	15 (4)	8 (2)
Fatigue	8 (4)	5 (2)	10 (3)	10 (3)
Headache	7 (3)	2 (<1)	8 (2)	1 (<1)
Hypotension	6 (3)	3 (1)	7 (2)	1 (<1)
ALT increased	5 (2)	2 (<1)	13 (4)	21 (6)
AST increased	4 (2)	2 (<1)	7 (2)	14 (4)
Arthralgia	3 (1)	0	6 (2)	22 (6)
Neutropenia	3 (1)	1 (<1)	20 (6)	3 (<1)
Rash	2 (<1)	3 (1)	9 (3)	48 (14)
Blood creatinine increased	1 (<1)	0	3 (<1)	14 (4)
Dehydration	1 (<1)	3 (1)	9 (3)	1 (<1)
GGT increased	0	2 (<1)	10 (3)	7 (2)
Rash maculo-papular	0	2 (<1)	3 (<1)	13 (4)

Post marketing experience

As of the data cut-off of 20 February 2015, 183 spontaneous SAE reports reporting a total of 292 SAEs in patients receiving combination therapy were received (Table 40). The most commonly affected body system from this analysis was the general disorders and administration site conditions SOC. Within this SOC, the most common SAEs were death (n=49), pyrexia (n=17), and disease progression (n=10); all other SAEs in this SOC were reported at a frequency of ≤ 4 events.

Table 40: Serious adverse events by SOC from spontaneous reports received cumulatively

System Organ Class	Total Events
Blood and lymphatic system disorders	7
Cardiac disorders	9
Ear and labyrinth disorders	1
Eye disorders	8
Gastrointestinal disorders	7
General disorders and administration site conditions	91
Hepatobiliary disorders	2
Infections and infestations	13
Injury, poisoning, and procedural complications	1
Investigations	7
Metabolism and nutrition disorders	7
Musculoskeletal and connective tissue disorders	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	40
Nervous system disorders	22
Psychiatric disorders	5
Renal and urinary disorders	13
Reproductive system and breast disorders	1
Respiratory, thoracic and mediastinal disorders	12
Skin and subcutaneous tissue disorders	11
Surgical and medical procedures	25
Vascular disorders	6
Total SAEs	**292**

Data Source: GSK ARGUS Database as of 20 February 2015

2.5.1. Discussion on clinical safety

The safety of trametinib in combination with dabrafenib has been evaluated in 2 Phase III studies, MEK115306 and MEK116513, where an analysis of the safety of trametinib in combination with dabrafenib was conducted in 209 and 350 patients, respectively, with BRAF V600 mutation positive unresectable or metastatic melanoma receiving trametinib (2 mg QD) and dabrafenib (150 mg BID) combination therapy (see section 5.1 combination therapy). The most common adverse reactions seen for combination therapy in both studies at ≥ 20 % include pyrexia, fatigue, nausea, chills, diarrhoea, cough, headache, hypertension, rash, vomiting and arthralgia. In study MEK115306 an additional adverse reaction seen at ≥ 20 % includes oedema peripheral. The safety of the combination therapy as reported for the phase III studies are supported by the safety results of the combination therapy obtained with the phase II study BRF113220 part C. See section 4.8 of the SmPC for the full list of ADRs and description of selected ADRs.

Some ADRs were found to be less frequent in the combination therapy compared to monotherapies. For study MEK115306, the most common AEs that occurred more often in the dabrafenib arm than in the combination therapy arm, were hyperkeratosis (35% vs 7%) and arthralgia (31% vs 26%, respectively), alopecia, PPES (hand-foot syndrome), palmoplantar keratoderma and skin papilloma. In MEK116513, arthralgia, rash and alopecia occurred in ≥30% of the patients in the vemurafenib arm compared to the combination therapy arm (51% vs 24%, 43% vs 22% and 39% vs 6%, respectively) and skin papilloma, PPES, hyperkeratosis, keratosis pilaris, pruritus, dry skin, photosensitivity reaction, sunburn and squamous cell carcinoma (cutaneous) were also reported more often in the monotherapy arm than in the combination therapy arm. The majority of the squamous cell carcinoma (cutaneous) events resolved following excision without dose modification or withdrawal of study drug.

In addition, grade 3 and 4 events occurred in similar proportions of patients in both treatment arms in MEK115306 (40% vs 46%; 5% vs 4%, respectively). In both MEK115306 and MEK116513 pyrexia (7%, 4% respectively) and hypertension (6%, 14% respectively) were among the most commonly reported grade 3 events for patients treated with combination therapy. However, the incidence of grade 3 events for squamous cell carcinoma (cutaneous) in both studies, and rash and keratoacanthoma in MEK116513, was lower for combination therapy in comparison to monotherapy BRAF.

Pyrexia was the most common SAE in the combination arms in both phase III studies (14-17%) but was not fatal, and most events resolved without dose changes, around 35% of the patients had a dose interruption and in 14% of the patients dosage was reduced because of pyrexia (see section 4.2 for dose reduction recommendations). When trametinib is used in combination with dabrafenib and the patient's temperature is ≥ 38.5°C please refer to the dabrafenib SmPC (section 4.2) for dose modifications for dabrafenib. No dose modification of trametinib is required when taken in combination with dabrafenib. Fever has been reported in clinical trials with trametinib as monotherapy and in combination with dabrafenib (see section 4.8). The incidence and severity of pyrexia are increased with the combination therapy (see dabrafenib SmPC section 4.4). In patients receiving trametinib in combination with dabrafenib, pyrexia may be accompanied by severe rigors, dehydration, and hypotension which in some cases can lead to acute renal insufficiency.

Another commonly reported SAE for patients treated with combination therapy in both studies was ejection fraction decrease (4-7%). Trametinib has been reported to decrease LVEF, when used as monotherapy or in combination with dabrafenib (see section 4.8). In clinical trials, the median time to onset of the first occurrence of left ventricular dysfunction, cardiac failure and LVEF decrease was between 2 and 5 months. No dose modification of dabrafenib is required when trametinib is taken in combination with dabrafenib.

If during treatment the QTc exceeds 500 msec, please refer to the dabrafenib SmPC (section 4.2) for dose modifications for dabrafenib. No dose modification of trametinib is required when taken in combination with dabrafenib. If during treatment the QTc exceeds 500 msec, please refer to the dabrafenib SmPC section 4.4.

Also, in the phase II study BRF113220 Part C two (incidence of 4%) fatal intracranial haemorrhages were reported. Like in the intracranial haemorrhage events in the phase III studies, also in these cases of fatal SAEs in the BRF113220 study they were not considered drug-related, however the phase II study was an open label study which might bias the determination of drug-related AEs Haemorrhagic events, including major haemorrhagic events and fatal haemorrhages, have occurred in patients taking trametinib as monotherapy and in combination with dabrafenib (see section 4.8). The majority of bleeding events were mild. Fatal intracranial haemorrhages have occurred for trametinib in combination with dabrafenib in 1% (3/209) of patients in study MEK115306 and in <1% (3/350) of patients in study MEK116513. In these clinical studies, the median time to onset of the first occurrence of haemorrhagic events was 94 days in both studies for the combination of trametinib and dabrafenib. The potential for these events in patients with unstable and/or symptomatic brain metastases not established as patients with these conditions were excluded from clinical trials. The risk of haemorrhage may be increased with concomitant use of antiplatelet or anticoagulant therapy. If haemorrhage occurs, patients should be treated as clinically indicated. Haemorrhagic events are currently included as an identified risk for the combination therapy in the RMP and will be monitored through routine pharmacovigilance. In addition, the risks of haemorrhagic events will be monitored through additional pharmacovigilance activities where the results of study BRF115532 (COMBI-AD), a randomised double blind study of dabrafenib in combination with trametinib versus two placebos in the adjuvant treatment of high risk BRAFV600 mutation positive melanoma after surgical resection will provide further longterm safety and study BRF117277, a phase II open label study of dabrafenib and trametinib in subjects with BRAF mutation positive melanoma that has metastasised to the brain. Both studies will focus on safety of patients with haemorrhagic events (see RMP).

Elevations in blood pressure have been reported in association with trametinib as monotherapy and in combination with dabrafenib, in patients with or without pre-existing hypertension (see SmPC section 4.8). In addition, safety in patients with treatment refractory hypertension defined as a blood pressure of systolic > 140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by antihypertensive therapy were excluded from study MEK115306 and have been included in the RMP as missing information related to trametinib. This will be monitored through routine risk minimisation measures.

Pulmonary embolism or deep vein thrombosis has been identified in the RMP as an important potential risk that can occur when trametinib is used in combination with dabrafenib. If patients develop symptoms of pulmonary embolism or deep vein thrombosis such as shortness of breath, chest pain, or arm or leg swelling, they should immediately seek medical care. Permanently discontinue trametinib and dabrafenib for life-threatening pulmonary embolism.

Pulmonary embolism and DVT will be monitored through routine risk minimisation measures.

In the phase III studies MEK115306 (n=209) and MEK116513 (n=350) with trametinib in combination with dabrafenib in patients with unresectable or metastatic melanoma, 56 patients (27 %) and 77 patients (22%) respectively were ≥ 65 years of age; 11 patients (5 %) and 21 patients (6%) respectively were ≥ 75 years of age. The proportion of patients experiencing AEs was similar in those aged < 65 years and those aged ≥ 65 years in both studies. Patients ≥ 65 years were more likely to experience SAEs and AEs leading to permanent discontinuation of medicinal product, dose reduction and dose interruption than those < 65 years.

Neutropenia and related events was found to be more common with combination treatment (14%) and in some patients more severe (grade 3 in 4-7%; grade 4 in 0-<1%) than compared with dabrafenib (4%) or

vemurafenib (3%) monotherapy. Therefore, neutropenia has been included as an important identified risk for combination therapy in the RMP and will be monitored through routine risk minimisation measures.

New malignancies, cutaneous and non-cutaneous, can occur when trametinib is used in combination with dabrafenib.

Cases of cuSCC (including keratoacanthoma) have been reported in patients treated with trametinib in combination with dabrafenib. Cases of cuSCC can be managed with excision and do not require treatment modification. Please refer to the dabrafenib SmPC (section 4.4).

New primary melanoma was reported in patients receiving trametinib in combination with dabrafenib. Cases of new primary melanoma can be managed with excision and do not require treatment modification. Please refer to the dabrafenib SmPC (section 4.4).

Based on its mechanism of action, dabrafenib may increase the risk of non-cutaneous malignancies when RAS mutations are present. When trametinib is used in combination with dabrafenib please refer to the dabrafenib SmPC (section 4.4). No dose modification of trametinib is required for RAS mutation positive malignancies when taken in combination with dabrafenib. Consider the benefits and risks before continuing treatment with dabrafenib in patients with a non-cutaneous malignancy that has a RAS mutation.

Dose modifications are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma (see dabrafenib SmPC for further details). If treatment related toxicities occur when trametinib is used in combination with dabrafenib then both treatments should be simultaneously dose reduced, interrupted or discontinued. Exceptions, where dose modifications are necessary for only one of the two treatments, are detailed below for pyrexia, uveitis, RAS mutation positive non cutaneous malignancies and QT prolongation (primarily related to dabrafenib), left ventricular ejection fraction (LVEF) reduction, retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED) and interstitial lung disease (ILD)/pneumonitis (primarily related to trametinib).

The risks of non-cutaneous malignancies will be monitored through additional pharmacovigilance activity where the results of study BRF115532 (COMBI-AD), a randomised double blind study of dabrafenib in combination with trametinib versus two placebos in the adjuvant treatment of high risk BRAFV600 mutation positive melanoma after surgical resection will provide further longterm safety data with focus on non-cutaneous malignancies.

No dose modifications are required for uveitis as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, withhold dabrafenib until resolution of ocular inflammation and then restart dabrafenib reduced by one dose level. No dose modification of trametinib is required when taken in combination with dabrafenib (see section 4.4).

Retinal vein occlusion (RVO) and Retinal pigment epithelial detachment (RPED):

In patients who are diagnosed with RVO, treatment with trametinib, whether given as monotherapy or in combination with dabrafenib, should be permanently discontinued. No dose modification of dabrafenib is required when trametinib is taken in combination with dabrafenib.

If uveitis is diagnosed, please refer to dabrafenib SmPC section 4.4. In patients who are diagnosed with RVO, treatment with trametinib should be permanently discontinued. No dose modification of dabrafenib is required when taken in combination with trametinib following diagnosis of RVO or RPED. No dose modification of trametinib is required when taken in combination with dabrafenib following diagnosis of uveitis.

Disorders associated with visual disturbance, including RPED and RVO, may occur with trametinib as monotherapy and in combination with dabrafenib. In clincial trials uveitis and iridocyclitis have also been reported in patients treated with trametinib in combination with dabrafenib.

No dose modification of dabrafenib is required when trametinib is taken in combination with dabrafenib for cases of ILD or pneumonitis.

In a Phase III trial, 2.4 % (5/211) of patients treated with trametinib monotherapy developed ILD or pneumonitis; all five patients required hospitalisation. The median time to first presentation of ILD or pneumonitis was 160 days (range: 60 to 172 days). In studies MEK115306 and MEK116513 < 1 % (2/209) and 1% (4/350), respectively, of patients treated with trametinib in combination with dabrafenib developed pneumonitis or ILD (see section 4.8). If trametinib is being used in combination with dabrafenib then therapy with dabrafenib may be continued at the same dose.

Trametinib should be used with caution in patients with moderate or severe hepatic impairment when administered as monotherapy or in combination with dabrafenib.

Hepatic adverse events have been reported in clinical trials with trametinib as monotherapy and in combination with dabrafenib (see section 4.8).

Rash has been observed in about 60 % of patients in trametinib monotherapy studies and in about 25% of patients in trametinib and dabrafenib combination studies MEK115306 and MEK116513 (see section 4.8).

Rhabdomyolysis has been reported in patients taking trametinib as monotherapy or in combination with dabrafenib (see section 4.8) and has been included in the RMP as an important identified risk. Rhabdomyolysis will be monitored through routine risk minimisation measures.

Renal failure has been identified in patients treated with trametinib in combination with dabrafenib in clinical studies. Please refer to the dabrafenib SmPC (section 4.4).

Pancreatitis has been reported in patients treated with trametinib in combination with dabrafenib in clinical studies. Please refer to the dabrafenib SmPC (section 4.4).

In non-clinical studies, the monotherapies have been shown to have developmental toxicity and teratogenic effects. In addition, the use of dabrafenib may render hormonal contraceptives less effective and therefore an alternative method of contraception, such as barrier methods, should be used when trametinib is used in combination with dabrafenib. Refer to the dabrafenib SmPC for further information. Effects on spermatogenesis have been observed in animals given dabrafenib. Male patients taking trametinib in combination with dabrafenib should be informed of the potential risk for impaired spermatogenesis, which may be irreversible. Refer to the dabrafenib SmPC for further information.

The percentage of patients treated with combination therapy who discontinued treatment due to AEs was 11% in the MEK115306 and 13% in the MEK116513 study suggesting that the combination therapy is well tolerated. Recommendations on treatment adjustments and management of ADRs that require dose reduction, treatment interruption or treatment discontinuation, are included in the SmPC section 4,2 (Table 1 and 2.

In clinical trials with the combination of trametinib and dabrafenib 11 patients reported trametinib overdose (4mg); no SAEs were reported.

2.5.2. Conclusions on clinical safety

The safety data submitted do not show any serious unexpected adverse reactions with the combination treatment dabrafenib/trametinib compared with dabrafenib and/or vemurafenib. The ADRs were in

general comparable to monotherapy, although slightly higher than the adverse events observed for the MEK and BRAF inhibitors in monotherapy and were manageable either through dose interruption or dose reduction. The greatest differences in incidences were seen for pyrexia and chills, which were more frequently reported for patients treated with dabrafenib and trametinib combination therapy than with dabrafenib or vemurafenib monotherapy. In contrast the incidence of squamous cell carcinoma (cuSCC) and keratoacanthoma was lower in the combination therapy arm than in the monotherapy arm of both studies. The risk of and actual occurrence of squamous cell carcinoma is an important additive burden for patients. Therefore a decrease of the incidence of this AE is considered an advantage of the combination therapy.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted RMPs.

On 9th July 2015 the PRAC considered by consensus that Mekinist (trametinib) RMP version 11 (dated 30 March 2015) and Tafinlar (dabrafenib) RMP version 7.0 (dated 27 March 2015) could be acceptable, provided that updated versions of these documents and satisfactory responses to the agreed List of Questions (LOQ) are submitted. The PRAC advice is attached.

On 15th July 2015 the Applicant submitted a satisfactory response to the LOQ, together with updated versions of the RMPs for trametinib (version 11.1, dated 14th July 2015) and dabrafenib (version 7.1, dated 14th July 2015).

The CHMP endorsed Mekinist (trametinib) RMP version 11.1 and Tafinlar (dabrafenib) RMP version 7.1 with the following contents (new text marked as bold and/or underline, deletions marked as strikethrough):

Safety concerns

The Summary of Safety Concerns is divided into two parts:

- Summary of safety concerns associated with **trametinib** or **dabrafenib monotherapy**
- Summary of safety concerns associated with **trametinib + dabrafenib combination therapy only**

Mekinist (trametinib)

Table 41: Summary of the Safety Concerns for Mekinist (trametinib)

Summary of safety concerns	
Important identified trametinib risks ~~related to both trametinib monotherapy and trametinib + dabrafenib combination therapy~~	• Skin toxicities (e.g., rash, dermatitis acneiform) • Diarrhoea • Left Ventricular Systolic Dysfunction (e.g., LVEF decreased and left ventricular dysfunction) • Ocular events (e.g., retinal vein occlusion, retinal pigment epithelial detachment~~, and uveitis~~) • Pneumonitis / Interstitial lung disease • Hepatic events (e.g., AST, ALT increased) • Hypertension • Oedema events (e.g., oedema peripheral) • Hypersensitivity • Rhabdomyolysis • Haemorrhagic events
Important identified risks related to trametinib+dabrafenib combination therapy only	• Neutropenia ~~Pyrexia~~ ~~Cutaneous SCC (cuSCC)~~ ~~Non-cutaneous secondary/recurrent malignancies~~ ~~New primary melanoma~~ ~~Pre-renal and Intrinsic Renal failure~~ ~~Pancreatitis~~ ~~Pulmonary embolism, deep vein thrombosis~~
Important potential trametinib risks ~~related to both trametinib monotherapy and trametinib+dabrafenib combination therapy~~	• Off-label use in resectable/resected melanoma (adjuvant treatment), in non-melanoma tumours harbouring a BRAFV600-mutation, melanoma 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

Summary of safety concerns	
	• Developmental toxicity • ~~Increased risk of dose adjustment, permanent treatment discontinuation~~ Use in elderly population (≥65 years)~~, as well as SAEs and Grade 3 AEs (combination only) in this population~~
Important potential risks related to trametinib+dabrafenib combination therapy only ~~**Important potential risks related to trametinib+dabrafenib combination therapy only**~~	• Pulmonary embolism, deep vein thrombosis
~~**Missing information related to trametinib monotherapy only**~~	• ~~Use in paediatric population (children less than 18 years)~~
Missing trametinib information ~~**Missing information related to trametinib monotherapy only related to both trametinib and trametinib+dabrafenib combination therapy**~~	• Use in paediatric population (children less than 18 years) • 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 • Risks in patients with ECOG 2-4 • Safety in patients with baseline QTc ≥480 msec QT prolongation, 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 mm Hg which cannot be controlled by anti-hypertensive therapy) ~~and abnormal cardiac valve morphology (combination only)~~ • 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 (i.e., Enzymes responsible for the hydrolytic cleavage of trametinib, Potential for saturation of P-gp and BCRP, Whether

Summary of safety concerns	
	trametinib is a substrate of OATP1B1 and OATP1B3 and whether trametinib is an inhibitor of OCT2, OAT1, or OAT3)

Tafinlar (dabrafenib)

Table 42: Summary of the Safety Concerns for Tafinlar (dabrafenib)

Summary of safety concerns	
Important dabrafenib identified risks ~~related to both dabrafenib monotherapy and dabrafenib + trametinib combination therapy~~	• cuSCC • New primary melanoma • Non-cutaneous secondary/recurrent malignancies • Pyrexia • Pre-renal and Intrinsic Renal failure • Hypersensitivity • Pancreatitis • Uveitis
Important identified risks related to dabrafenib + trametinib combination therapy only	~~• Skin toxicities (e.g., rash, dermatitis acneiform)~~ ~~Diarrhoea~~ ~~Left ventricular systolic dysfunction (e.g., LVEF decreased and left ventricular dysfunction)~~ ~~Ocular events (e.g., retinal vein occlusion, retinal pigment epithelial detachment, and uveitis)~~ ~~Pneumonitis/Interstitial lung disease~~ ~~Hepatic events (e.g., AST, ALT, increased)~~ ~~Hypertension~~ ~~Oedema events (e.g., oedema peripheral)~~ ~~Haemorrhagic events~~ • Neutropenia ~~Pulmonary embolism, Deep vein thrombosis~~ ~~Rhabdomyolysis~~

Summary of safety concerns	
Important potential dabrafenib risks ~~related to dabrafenib monotherapy only~~ ~~**Important potential risks related to both dabrafenib monotherapy and dabrafenib + trametinib combination therapy**~~	• ~~Non-specific cardiac toxicity~~ • ~~Hyperglycaemia~~ • Testicular Toxicity • ~~Increased risk for Grade 3 AEs, SAEs and dose adjustments~~Use in elderly population (≥65 years) ~~as well as increased risk of permanent treatment discontinuations (combination only) and Grade 4 AEs (dabrafenib monotherapy only) in this population~~ • Off-label use in resectable/resected melanoma (adjuvant treatment), non-melanoma tumour harbouring a BRAFV600-mutation, in combination with other anti-cancer agents, or when non-validated tests are used • Paediatric effects • Potential for QT Prolongation • Developmental toxicity • Drug-drug interactions • Photosensitivity
Important potential risks related to dabrafenib + trametinib combination therapy only	Pulmonary embolism, Deep vein thrombosis~~Impaired female fertility~~ • ~~Pulmonary embolism, Deep vein thrombosis~~
Missing dabrafenib information ~~related to dabrafenib monotherapy and dabrafenib + trametinib combination therapy~~	• Use in patients with reduced cardiac function or symptomatic NYHA 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 • Risks in patients with ECOG 2-4 • Rare adverse reactions • 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

Summary of safety concerns	
	abnormal or worse)
~~Missing information related to dabrafenib + trametinib combination therapy only~~	~~• Safety in patients with history of RVO or CSR/RPED~~ ~~Safety in patients with history of pneumonitis or interstitial lung disease~~ ~~• Safety in patients with treatment refractory hypertension (blood pressure of systolic > 140 mmHg and/or diastolic > 90 mmHg which cannot be controlled by anti hypertensive therapy)~~

Pharmacovigilance plan

Mekinist (trametinib)

Table 43: Ongoing and planned studies in the pharmacovigilance development plan for Mekinist (trametinib)

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
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 Hepatic impaired patients	Planned start 2Q2014	Final report projected in 4Q2017
201711 Annual Reports for Cardiomyopathy-related adverse reactions (Clinical, 3)	Cumulative safety analyses will be submitted annually, and for one year after the last patient has completed clinical trial treatment, to identify and characterize the risk of cardiomyopathy and subsequent sequelae, including safety evaluations adequate to inform labeling of patient populations at highest	Cumulative annual safety analyses of Left ventricular systolic dysfunction	Ongoing	Final report projected in 4Q2020

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
	risk for developing these toxicities and to provide evidence-based dose modification and monitoring recommendations, in all ongoing and subsequently initiated randomized controlled clinical trials through 2020 that use trametinib alone or in combination with other anti-cancer drugs.			
GSK1120212B: *In Vitro* Phototoxicity Assay with 3T3 Cells (Preclinical, 3)	An in vitro assay to better characterize the risk of photosensitivity reactions	Skin toxicity (Photosensitivity)	Study start 2Q2014	Final report completed and in review under a separate variation procedure~~complete 1Q2015~~
A repeat study to investigate the enzymes responsible for the hydrolytic cleavage of trametinib (Preclinical, 3)	A repeat study to investigate the enzymes responsible for the hydrolytic cleavage of trametinib (to help predict drug-drug interactions by this route)	Drug-drug interactions	Study start 2Q2014	Final report completed and in review under a separate variation procedure~~complete 1Q2015~~
Studies investigating the potential for saturation of P-gp and BCRP using MDCKII-MDR1 and MDCKII-BCRP cell lines at clinically relevant concentrations (Preclinical, 3)	Studies investigating the potential for saturation of P-gp and BCRP using MDCKII-MDR1 and MDCKII-BCRP cell lines at clinically relevant concentrations (to better characterise the risk of drug-drug interactions)	Drug-drug interactions	Study start 2Q2014	Final report completed and in review under a separate variation procedure~~complete 1Q2015~~
Studies determining whether trametinib is a substrate of OATP1B1	Studies determining whether trametinib is a substrate of OATP1B1	Drug-drug interactions	Study start 2Q2014	Final report completed and in review under a

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
and OATP1B3 and whether trametinib is an inhibitor of OCT2, OAT1, or OAT3 (Preclinical, 3)	and OATP1B3 and whether trametinib is an inhibitor of OCT2, OAT1, or OAT3 (to better characterise the risk of drug-drug interactions)			separate variation procedure~~complete 1Q2015~~
MEK114655: TQT Study (Clinical, 3)	To evaluate the effect of trametinib on ECG parameters, in particular cardiac repolarization	QT prolongation	Started 3Q2012	Final report complete 4Q2015
~~201712 Ocular Toxicity (Clinical, 3)~~	~~Integrated safety analyses from a randomized controlled clinical trials with trametinib to identify and characterize the risk of retinal pigmented epithelial detachments (RPED),~~	~~Ocular Toxicity~~	~~3Q2013~~	~~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	Ongoing	Primary study report projected ~~3~~1Q201~~7~~8
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	Ongoing	Final report complete 4Q2017

*Category 1 study: imposed activity considered key to the benefit risk of the product.
Category 2 study: specific obligation
Category 3 study: required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Table 44: Ongoing and planned studies in the pharmacovigilance development plan for Tafinlar (dabrafenib)

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
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 interaction	Ongoing	Final report projected in 3Q2017
BRF113773: TQT Study (Clinical, 3)	To evaluate the effect of dabrafenib on ECG parameters, in particular cardiac repolarization	QT prolongation	~~Started; planned finish 1Q2015~~Ongoing	Final report 2Q2016
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	~~Started; primary analysis finish 4Q2015~~Ongoing	Primary study report projected ~~1~~1Q201~~78~~
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 interaction	Ongoing	Final report 2Q2017
BRF113683 (BREAK-3) (Clinical, 3)	A Phase III randomized, open-label study comparing dabrafenib	Long-term safety with focus on non-cutaneous	Ongoing~~Started; study finish~~	Final report projected 1Q2017

	to DTIC in previously untreated subjects with BRAF mutation positive advanced (Stage III) or metastatic (Stage IV) melanoma.	malignancies	~~projected 2Q2016~~	
BRA115947 Hepatic and Renal Impairment (Clinical, 3)	NCI Sponsored Phase I and PK Study to obtain dosing recommendation in patients with severe renal or moderate to severe hepatic impairment	Renal and hepatic impaired patients	Ongoing	Final report 4Q2019
BRF116893 Photosensitivity Study (Clinical, 3)	A Phase IIa/IIb GSK/Novartis-supported study - Evaluation of photosensitivity in Dabrafenib or Vemurafenib treated metastatic melanoma patients	Photosensitivity	Ongoing~~Planned start 1Q2014~~	Final report projected in 1Q2018
~~201709~~ ~~Cardiac valve abnormality (clinical; 3)~~	~~A non-interventional study to perform ECHO analyses from randomized controlled trials of dabrafenib to evaluate the potential for cardiac valve abnormalities~~	~~Cardiac valve abnormality~~	~~Ongoing~~	~~Final report projected in 4Q2020~~
201710 Secondary malignancies (clinical; 3)	A non-interventional study to perform evaluation of secondary malignancies in patients treated with dabrafenib in randomized, controlled trials	Secondary malignancies	Ongoing	Final report projected in 4Q2020

*Category 1 study: imposed activity considered key to the benefit risk of the product.
Category 2 study: specific obligation
Category 3 study: required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Risk minimisation measures

Mekinist (trametinib)

Table 45: Summary Table of Risk Minimisation Measures for Mekinist (trametinib)

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important ~~identified~~ Identified Trametinib ~~risks~~ Risks ~~related to both trametinib monotherapy and trametinib + dabrafenib combination therapy~~		
Skin toxicities (e.g., Rash, Dermatitis acneiform)	• Warning in the product labelling for rash • ADRs in the product labelling for rash and other skin-related toxicities • Guidance for management in protocols~~, product labelling~~ • Information for patients in PIL • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Diarrhoea	• ADR in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Left Ventricular Systolic Dysfunction (e.g., LVEF decreased and LV dysfunction)	• Warning in the product labelling • ADR in product labelling • Guidance for management in protocols, product labelling • Information for patients in PIL • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	of anti-cancer medicinal products.	
Ocular events (e.g., retinal vein occlusion, retinal pigment epitheltial detachment)	• Warning in product labelling • ADRs in product labelling • Guidance for management in protocols, product labelling • Information for patients in PIL • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Pneumonitis / Interstitial lung disease	• Warning in product labeling • ADR in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Hepatic events (e.g., AST and ALT increased)	• Warning in product labeling • ADR in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Hypertension	• Warning in product labeling • ADR in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	
Oedema events (e.g., oedema peripheral)	• ADR in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Hypersensitivity	• Contraindication in product labelling • ADR in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Rhabdomyolysis	• Warning and ADR in product labelling • Information for patients in PIL • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products	None
Haemorrhagic events	• Warning and ADR in the product labelling • Information for patients in PIL • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products	None
Important Identified risks related to trametinib and dabrafenib combination therapy only		
~~**Pyrexia**~~	~~• Referred to dabrafenib product labelling~~ ~~• Warning in product labelling~~	~~None~~

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• ADRs in product labelling • Guidance for management in protocols, product labelling • Information for patients in PIL • Prescription only medicine • Treatment with trametinib in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	
cuSCC	• Referred to dabrafenib product labelling • Warning in product labelling • ADRs in product labelling • Guidance for management in protocols, product labelling • Information for patient in PIL • Prescription only medicine • Treatment with trametinib in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Non-cutaneous secondary/recurrent malignancies	• Referred to dabrafenib product labelling • Warning in product labelling • Information for patient in PIL • Prescription only medicine • Treatment with trametinib in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
New primary melanoma	• Referred to dabrafenib product labelling • Warning and ADR in product labelling • Guidance for management in protocols, product labelling • Information for patient in PIL	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Prescription only medicine • Treatment with trametinib in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	
Pre-renal and intrinsic renal failure	• Referred to dabrafenib product labelling • Referred to in warning for pyrexia in product labelling • ADRs in product labelling • Guidance for pyrexia management in protocols, product labelling • Information for patient in PIL • Prescription only medicine • Treatment with trametinib in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Pancreatitis	• Referred to dabrafenib product labelling • ADRs in product labelling • Information for patient in PIL • Prescription only medicine • Treatment with trametinib in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Pulmonary embolism, deep vein thrombosis	• Warning in product labelling • Prescription only medicine • Treatment with trametinib in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products	None
Neutropenia	• ADR in the product labelling • Information for patient in PIL • Prescription only medicine • Treatment with trametinib in combination	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	with dabrafenib should only be initiated by a physician experienced in the administration of anti-cancer medicinal products.	
Important ~~potential~~ Potential Trametinib ~~risks~~ Risks ~~related to both trametinib monotherapy and trametinib + dabrafenib combination therapy~~		
Off-label use in resectable/resected melanoma (adjuvant treatment), in non-melanoma tumours harbouring a BRAF V600-mutation, melanoma 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	• Information in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Hepatic failure	• Warning in product labelling around hepatic events • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products	None
Impaired female fertility	• Information in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products	None
Developmental toxicity	• Information in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with trametinib monotherapy	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	
~~Increased risk of dose adjustment, permanent treatment discontinuation~~Use **in elderly population (≥65 years)**~~, as well as SAEs and Grade 3 AEs (combination only) in this population~~	• Information in product labelling • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products	None
Important potential risks related to trametinib + dabrafenib combination therapy only		
Pulmonary embolism, deep vein thrombosis	• Warning in product labelling • Prescription only medicine • Treatment with trametinib in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products	None
~~Testicular Toxicity~~	~~• Referred to dabrafenib product labelling~~ ~~• Information in product labelling~~ ~~• Information for patients in PIL~~ ~~• Prescription only medicine~~ ~~• Treatment with trametinib in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.~~	~~None~~
~~Drug-drug interactions~~	~~• Referred to dabrafenib product labelling~~ ~~• Information in product labelling~~ ~~• Information for patients in PIL~~ ~~• Prescription only medicine~~ ~~• Treatment with trametinib in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.~~	~~None~~

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
~~Potential for QT prolongation~~	~~Referred to dabrafenib product labelling~~ ~~Warning in product labelling~~ ~~Prescription only medicine~~ ~~Treatment with trametinib in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.~~	~~None~~
~~Paediatric Effects~~	~~Prescription only medicine~~ ~~Treatment with trametinib in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.~~	~~None~~
~~Missing information related to trametinib monotherapy only~~		
~~Use in paediatric population (children less than 18 years)~~	~~Information in product labelling~~ ~~Information for patients in PIL~~ ~~Prescription only medicine~~ ~~Treatment with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.~~	~~None~~
Missing Trametinib I~~nformation related to both trametinib and trametinib + dabrafenib combination therapy~~		
Use in paediatric population (children less than 18 years)	• Information in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Use in patients with reduced cardiac function or symptomatic Class II, III, or IV heart failure (NYHA functional classification system)	• Information related to cardiac conditions in the label • Information on heart problems for patients in PIL • Prescription only medicine • Treatment with trametinib monotherapy	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	
Safety in patients with severe renal impairment	• Information in product labelling • Information for patients in the PIL • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Safety in patients with moderate to severe hepatic impairment	• Information in product labelling • Information for patients in the PIL • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Non-White population	• Statement in product labelling that there are insufficient data to evaluate the potential effect of race on trametinib pharmacokinetics • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Pregnancy and risks in breast-feeding	• Information in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in patients with ECOG 2-4	• No data in this population is available • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Safety in patients with baseline QTc ≥480 msec QT prolongation, 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 mm Hg which cannot be controlled by anti-hypertensive therapy~~) and abnormal cardiac valve morphology (combination only)~~	• Information in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products	None
Safety in patients with history of retinal vein occlusion or central serous retinopathy (reclassified as Retinal Pigment Epithelial Detachment, RPED)	• Information in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products	None
Safety in patients with history of pneumonitis or interstitial lung disease	• Information in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products	None
Drug-drug interactions (i.e., Enzymes responsible for the hydrolytic cleavage of trametinib,	• Information in product labelling • Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Potential for saturation of P-gp and BCRP, Whether trametinib is a substrate of OATP1B1 and OATP1B3 and whether trametinib is an inhibitor of OCT2, OAT1, or OAT3)	• Treatment with trametinib monotherapy and in combination with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products	

Tafinlar (dabrafenib)

Table 46: Summary table of Risk Minimisation Measures for Tafinlar (dabrafenib)

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important i~~I~~dentified dabrafenib risks ~~related to both dabrafenib monotherapy and dabrafenib + trametinib combination therapy~~		
cuSCC	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Warning in product labelling • ADR in product labelling • Guidance for management in protocols, product labelling • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products. • Information for patients in PIL	**None**
New primary melanoma	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Warning in product labelling • ADR in product labelling • Guidance for management in protocols, product labelling • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be	**None**

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products. • Information for patients in PIL	
Non-cutaneous secondary/recurrent malignancies	~~• Dabrafenib monotherapy and in combination with trametinib:~~ • Warning in product labelling • Described in Section 4.8 of the SmPC • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products. • Information on monitoring for patients in PIL	**None**
Pyrexia	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Warning in product labelling • ADR in product labelling • Guidance for management in protocols, product labelling • Information for patients in PIL • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	**None**
Pre-renal and Intrinsic Renal failure	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Referred to in warning for pyrexia in	**None**

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	product labelling • Warning in product labelling • ADR in product labelling • Guidance for pyrexia management in protocols, product labelling • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products. • Information for patients in PIL	
Hypersensitivity	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Contraindication in product labelling • ADR in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	**None**
Pancreatitis	~~• Dabrafenib monotherapy and in combination with trametinib:~~ • Warning in product labelling • ADR in product labelling • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer	**None**

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	medicinal products. • Information for patients in PIL	
Uveitis	~~• Dabrafenib monotherapy and in combination with trametinib:~~ • Warning in product labelling • ADR in product labelling • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products. • Information for patients in PIL	**None**
Identified risks related to dabrafenib + trametinib combination therapy only		
~~**Skin toxicities (e.g., Rash, Dermatitis acneiform)**~~	~~Dabrafenib + trametinib combination therapy:~~ ~~Warning in the product labelling for rash~~ ~~ADRs in the product labelling for rash and other skin-related toxicities~~ ~~Guidance for management in protocols, product labelling~~ ~~Information for patients in PIL~~ ~~Prescription only medicine~~ ~~Treatment with dabrafenib in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.~~	~~**None**~~
~~**Diarrhoea**~~	~~Dabrafenib + trametinib combination therapy:~~ ~~ADR in product labelling~~ ~~Information for patients in PIL~~ ~~Prescription only medicine~~ ~~Treatment with dabrafenib in combination with trametinib should only be initiated and~~	~~**None**~~

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	supervised by a physician experienced in the administration of anti-cancer medicinal products.	
Left Ventricular Systolic Dysfunction (e.g., LVEF decreased and LV dysfunction)	Dabrafenib + trametinib combination therapy: Warning in the product labelling ADR in product labelling Guidance for management in protocols, product labelling Information for patients in PIL Prescription only medicine Treatment with dabrafenib in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Ocular events (e.g., retinal vein occlusion, retinal pigment epithelial detachment, and uveitis)	Dabrafenib + trametinib combination therapy: Warning in product labelling for visual impairment ADRs in product labelling Guidance for management in protocols, product labelling Information for patients in PIL Prescription only medicine Treatment with dabrafenib in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Pneumonitis/Interstitial lung disease	Dabrafenib + trametinib combination therapy: Warning in product labelling ADR in product labelling Information for patients in PIL Prescription only medicine Treatment with dabrafenib in combination	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	
Hepatic events (e.g., AST, ALT increased)	Dabrafenib + trametinib combination therapy: Warning in product labelling ADRs in product labelling Information for patients in PIL Prescription only medicine Treatment with dabrafenib in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Hypertension	Dabrafenib + trametinib combination therapy: Warning in product labelling ADR in product labelling Information for patients in PIL Prescription only medicine Treatment with dabrafenib in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Oedema events (e.g., oedema peripheral)	Dabrafenib + trametinib combination therapy: ADR in product labelling Information for patients in PIL Prescription only medicine Treatment with dabrafenib in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Haemorrhagic events	Dabrafenib + trametinib combination	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	~~therapy:~~ ~~Warning in product labelling~~ ~~ADR in the product labelling~~ ~~Information for patients in PIL~~ ~~Treatment with dabrafenib in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products~~	
Neutropenia	~~Dabrafenib + trametinib combination therapy:~~ • ADR in the product labelling • Information for patients in PIL • Prescription only medicine • Treatment with dabrafenib in combination with trametinib should only be initiated by a physician experienced in the administration of anti-cancer medicinal products	**None**
~~**Pulmonary embolism, Deep vein thrombosis**~~	~~Dabrafenib + trametinib combination therapy:~~ ~~Warning in the product labelling~~ ~~Information for patients in PIL~~ ~~Prescription only medicine~~ ~~Treatment with dabrafenib in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products~~	~~**None**~~
~~**Rhabdomyolysis**~~	~~Dabrafenib + trametinib combination therapy:~~ ~~• Warning in product labelling~~ ~~• ADRs in product labelling~~ ~~• Prescription only medicine~~ ~~Information for patients in PIL~~ ~~• Treatment with dabrafenib should only be initiated and supervised by a~~	~~**None**~~

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	~~physician experienced in the administration of anti-cancer medicinal products~~	
Important potential dabrafenib risks ~~related to dabrafenib monotherapy only~~		
Non-specific Cardiac Toxicity	~~Dabrafenib monotherapy:~~ • Prescription only medicine • Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products	**None**
~~**Hyerglycaemia**~~	~~Dabrafenib monotherapy:~~ ~~• ADR in the product labelling~~ ~~• Information for patients in PIL~~ ~~• Prescription only medicine~~ ~~• Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.~~	~~**None**~~
~~**Important potential dabrafenib risks related to both dabrafenib monotherapy and dabrafenib + trametinib combination therapy**~~		
Testicular Toxicity	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Information in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	**None**
~~**Increased risk for Grade 3 AEs, SAEs and dose adjustment** Use~~ **in elderly population (≥65 years)** ~~**as well as increased risk of permanent treatment**~~	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Information in product labelling	**None**

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
~~discontinuations (combination only) and Grade 4 AEs (dabrafenib monotherapy only) in this population~~	• Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	
Off-label use in resectable/resected melanoma (adjuvant treatment), non-melanoma tumours harbouring a BRAF V600-mutation, in combination with other anti-cancer agents, or when non-validated tests are used	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Information in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	**None**
Paediatric effects	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Information in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	**None**
Potential for QT Prolongation	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Warning in product labelling • ADR in product labelling (dabrafenib monotherapy) • Information for patients in PIL	**None**

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	
Developmental Toxicity	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Information in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products	**None**
Drug-drug interaction	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Warning in product labelling • Additional information in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Photosensitivity	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	
Potential risks related to dabrafenib + trametinib combination therapy only		
Pulmonary embolism, Deep vein thrombosis	• Warning in the product labelling • Information for patients in PIL • Prescription only medicine • Treatment with dabrafenib in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products	None
~~Impaired Female Fertility~~	~~Dabrafenib + trametinib combination therapy:~~ ~~Information for patients in product labelling~~ ~~Information for patients in PIL~~ ~~Prescription only medicine~~ ~~Treatment with dabrafenib in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products~~	~~None~~
Missing dabrafenib information ~~related to both dabrafenib monotherapy and dabrafenib + trametinib combination therapy~~		
Use in patients with reduced cardiac function or symptomatic NYHA Class II, III, or IV heart failure (NYHA functional classification system)	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Information related to cardiac conditions in product labelling • Information on heart problems for patients in PIL • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	medicinal products.	
Safety in patients with severe renal impairment	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Information in product labelling • Information for patients in the PIL • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	**None**
Safety in patients with moderate to severe hepatic impairment	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Information in product labelling • Information for patients in the PIL • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	**None**
Non-White population	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Statement in product labelling that there are insufficient data to evaluate the potential effect of race on dabrafenib pharmacokinetics • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	**None**

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Pregnancy and risks in breast-feeding	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Information in product labelling • Information for patients in PIL • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	**None**
Use in patients with ECOG 2-4	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	**None**
Rare adverse reactions	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Ongoing evaluation of adverse events in patients • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	**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	~~Dabrafenib monotherapy and in combination with trametinib:~~ • Information related to cardiac conditions • Information on heart problems for	**None**

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
weeks; and abnormal cardiac valve morphology (moderately abnormal or worse)	patients in PIL ~~Information in product labelling~~ ~~Information for patients in PIL~~ • Prescription only medicine • Treatment with dabrafenib monotherapy and in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	
~~**Missing information related to dabrafenib + trametinib combination therapy only**~~		
~~**Safety in patients with history of RVO or CSR/RPED**~~	~~Dabrafenib + trametinib combination therapy:~~ ~~Warning for visual impairment in product labelling~~ ~~Information for patients in PIL~~ ~~Prescription only medicine~~ ~~Treatment with dabrafenib in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products~~	~~**None**~~
~~**Safety in patients with history of pneumonitis or interstitial lung disease**~~	~~Dabrafenib + trametinib combination therapy:~~ ~~Information in product labelling~~ ~~Information for patients in PIL~~ ~~Prescription only medicine~~ ~~• Treatment with dabrafenib in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products~~	~~**None**~~
~~**Safety in patients with treatment refractory hypertension (blood pressure of systolic > 140 mmHg**~~	~~Dabrafenib + trametinib combination therapy:~~	~~**None**~~

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
and/or diastolic > 90 mmHg which cannot be controlled by anti-hypertensive therapy)	• Information in product labelling • Information for patients in PIL • Prescription only medicine Information in product labelling Information for patients in PIL Prescription only medicine • Treatment with dabrafenib in combination with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products	

Overall comment

The proposed risk minimisation measures for both trametinib or dabrafenib monoterapy and the combination therapy remain sufficient to minimise the risks of the products in the proposed indication.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.6 4.8, 5.1, 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

- As the MEKINIST PL from initial MAA contained language for the co-administration of both trametinib and dabrafenib when the readability testing was conducted and was found to be acceptable, there is no further consultation with target patient groups is required for the PL included.
- The TAFINLAR PL was approved with initial MAA on 26th August 2013. The information proposed in the PL submitted with this variation contain minimal changes, maintaining the currently approved layout and format and is not considered to require further consultation with target patient groups.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The study MEK115306 showed a PFS with a HR of 0.67 (95% CI 0.53, 0.84; p<0.001) and a prolongation of median PFS of 2.2 months (11.0 months for the combination therapy arm and 8.8 months for the monotherapy arm). The updated OS results also showed a statistically significant difference with a HR = 0.71 (95% CI: 0.55, 0.92, p=0.011) for OS in favour of the combination therapy. The PFS and OS results

were considered clinical relevant. Subgroup analysis and sensitivity analysis (OS and PFS analysis with Cox model accounting for significant prognostic factor like ECOG score, visceral disease, number of disease sites and gender) demonstrated consistent results in the ITT population. The robustness of the data was supported by the study MEK116513, which showed similar results (see clinical discussion).

Uncertainty in the knowledge about the beneficial effects

In both phase III studies, patients who did not receive previous treatment for metastatic disease were included in the study population. Phase II study BRF113220 included a low number of patients who had progressive disease on dabrafenib monotherapy. Of these patients (cross over population) around 10% showed responses on combination therapy after they had progressive disease with dabrafenib monotherapy. It was noted that the efficacy observed in pre-treated patients with BRAF inhibitors was lower than in naïve patients who had not received prior BRAF inhibitor therapy. Therefore, the CHMP considered that the efficacy data for combination therapy in patients that progressed on prior BRAF inhibitor monotherapy was too limited to draw any conclusion. However, it is acknowledged that patients may still derive some benefit from the combination therapy. Therefore, the indication was not restricted but a warning statement on the lower efficacy in this patient population has been included in section 4.4 and 5.1 of the SmPC.

It is uncertain which sequencing of treatment may be best for melanoma patients as new emerging treatments for melanoma (eg immunotherapies) have been recently been approved that may change the landscape of treatment strategies and clinical paradigms in the management of melanoma patients. Thus, a statement has been included in section 4.4 of the SmPC to advise prescribers that other treatment options could be considered before treatment with the combination in this prior BRAF inhibitor treated population and that sequencing of treatments following progression on a BRAF inhibitor therapy has not been established.

Patients with brain metastases were not included in the studies MEK115306 and MEK116513 and no further data is available. There is a study ongoing which will examine the efficacy of the combination therapy in patients with active brain metastases (COMBI-MB) and this has been included as a post-authorisation commitment in the RMP. The SmPC has been updated to include a warning in section 4.4 and information on the lack of patients with brain metastases in section 5.1.

Risks

Unfavourable effects

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.

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, QT prolongation and hepatic events. These ADRs are managed through appropriate recommendations in the SmPC and monitored with routine risk minimisation measures.

Squamous cell carcinoma of the skin (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, squamous cell carcinoma (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%). The majority of squamous cell carcinoma (cutaneous) events resolved

following excision without dose modification or withdrawal of study drug.

Uncertainty in the knowledge about the unfavourable effects

Six patients in the phase III studies treated with combination therapy died due to bleeding events and two cases (4%) were also reported in the phase II study BRF113220 Part C. Although none of these events were considered related to study treatment by the investigator, the contribution of trametinib and/or dabrafenib to haemorrhages could not be ruled out. Therefore, haemorrhagic events are included in the RMP as identified risks and management of these events will be performed through the recommendations in the SmPC and monitoring through routine risk minimisation measures.

Effects Table

Table 47: Effects table for trametinib and dabrafenib combination in unresectable or metastatic melanoma with BRAF V600 mutation (data cut-off study MEK115306: 12 Jan 2015, study MEK 116513: 17 Apr 2014)

	Short Description	Unit	Treatment Both studies: trametinib + dabrafenib	Control MEK115306: dabrafenib MEK116513: vemurafinib	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	Time from randomization until PD or death due to any cause per INV in ITT population	Months (KM median ; 95% CI)	**MEK115306** (primary endpoint, n=211) 11.0 (8.0, 13.9) HR of 0.67 (95% CI 0.53, 0.84; p<0.001)	**MEK115306** (n=212) 8.8 (5.9, 9.3)	PFS and ORR benefit of combination therapy in both studies and significant OS improvement in MEK115306 study. Supported by improvement in QoL, sensitivity- and subgroup analyses (except for subgroup analyses in ECOG 1 pts and pts without visceral disease in MEK116513 study). Uncertainties: - OS data of study MEK116513 were still immature at the moment of initial submission, however updated OS data (dated 13 March 2015) has been submitted that confirm the results of the previous analysis (dated 17 April 2014). The updated OS analysis is based on 44% of the events in the combination therapy arm and 55% of the events in the monotherapy arm. The table is updated whit OS data of 13 March 2015. - Efficacy uncertain (1) in patients previously treated with BRAFi monotherapy in first line (2) for patients with brain metastasis, the efficacy of combination	See clinical efficacy section and discussion
			MEK116513 (n=352) 11.4 (9.9, 14.9)	**MEK116513** (n=352) 7.3 (5.8, 7.8)		
OS	Time from randomization to death due to any cause	Months (KM median ; 95% CI)	**MEK115306** 25.1 (19.2, NR) HR of 0.71 (95% CI 0.55, 0.93; p=0.011)	**MEK115306** 18.7 (15.2, 23.7)		
			MEK116513 (primary endpoint) 25.6 (22.6, NR) (HR 0.0.66; 95% CI 0..53, 0.81; p<0.001)	**MEK116513** 18.0 (15.6, 20.7)		
ORR	Percentage of patients with CR+ PR at any time	Percentage (95% CI)	**MEK115306** 69% (61.8, 74.8)	**MEK115306** 53% (46.3, 60.2)		

	Short Description	Unit	Treatment Both studies: trametinib + dabrafenib	Control **MEK115306**: dabrafenib **MEK116513**: vemurafinib	Uncertainties / Strength of evidence	References
			MEK116513 64% (59.1, 69.4)	**MEK116513** 51% (46.1, 56.8)	therapy in patients with brain metastasis is studied in the still ongoing COMBI-MB study - efficacy not compared with approved immotherapy options (e.g. ipilimumab or nivolumab) - efficacy of dabrafenib+trametinib combination therapy after progression on immunotherapy is not investigated.	
Unfavourable Effects						
AEs (e.g. pyrexia, nausea, chills, diarrhoea, fatigue, headache)	Incidence as percentage of patients involved	Percentage	**MEK115306** 97% AE leading to permanent discontinuation: 11%	**MEK115306** 97% AE leading to permanent discontinuation: 7%	Uncertainties: - the percentage of patients with the AEs squamous cell carcinoma (SCCcu) and keratoacanthoma. An decreased incidence of such squamous cell carcinoma is considered a benefit of the combination therapy - AEs leading to permanent discontinuation or dose modification and SAEs more frequent in pts ≥ 65 years. - 6 fatal bleeding events (in total 104 bleeding events in the experimental arm of both studies), considered not treatment related by INV. However contribution of trametinib and/or dabrafenib cannot be ruled out. The occurrence of bleeding events will be followed up post approval with routine pharmacovigilance activities.	See clinical safety section and discussion.
			MEK116513 98% AE leading to permanent discontinuation: 13%	**MEK116513** 99% AE leading to permanent discontinuation: 12%		
AE of special interest	Squamous cell carcinoma keratonacathoma		1% 1%	5-10% 2-9%		
SAEs (e.g. pyrexia, LVEF decrease, chills)	Incidence as percentage of patients involved	Percentage	**MEK115306** 42%	**MEK115306** 37%		
			MEK116513 37%	**MEK116513** 35%		

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The prognosis of patients with advanced melanoma is still poor, in spite of recently approved new therapies. The combination of dabrafenib and trametinib in the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation has demonstrated clinical benefit in a patient population with a high unmet need. The results for OS and PFS were statistically significant and clinically relevant. This is supported by ORR and DoR data.

Overall, combination treatment is associated with a higher incidence of ADRs, including grade 3 events. However, the safety and tolerability of the combination treatment is considered acceptable and manageable. In addition, the percentage of patients with squamous cell carcinoma (cuSCC) and keratoacanthoma seemed to be lower than that observed with monotherapy treatment. The risk and the actual occurrence of cuSCC is an important additive burden for patients. Therefore the decreased incidence of such squamous cell carcinoma is considered a benefit of the combination therapy.

Benefit-risk balance

The CHMP considers that the benefits of dabrafenib and trametinib combination therapy in adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation outweigh the risks. Therefore, the CHMP considers that the benefit risk balance is positive.

Discussion on the Benefit-Risk Balance

The combination of trametinib and dabrafenib is supported by non-clinical and clinical data where blocking the MAPK kinase pathway at two separate levels is expected to improve efficacy. The strength of the evidence has been shown in the two pivotal studies MEK115306 and MEK116513 where a clinically relevant improvement in PFS and OS has been demonstrated. Both studies included patients who had not been previously treated with BRAF inhibitors. For patients who were treated with a BRAF inhibitor as monotherapy (dabrafenib or vemurafenib), only limited efficacy data exist and the response rates in patients who had progressed after treatment with a BRAF inhibitor was lower than for patients that were previously untreated. Taking into account that in clinical practice, a proportion of patients will have been previously treated with other BRAF or MEK inhibitors, the CHMP highlighted that the combination treatment may not provide the same clinical benefit in those patients as what has been observed in the clinical trials which enrolled naïve patients not previously treated with MAPK kinase pathway inhibitors and that clinical benefit has not been demonstrated in this patient population. Nevertheless, the indication was not restricted as it was considered that patients previously treated with BRAF inhibitors could still derive some benefit from the combination therapy.

New therapeutic options have been approved recently for melanoma, some targeting the immune system instead of the melanoma cancer cells. Immunotherapeutic agents such as ipilimumab, pembrolizumab and nivolumab are not thought to interfere with the RAS, RAF, MEK, ERK signalling pathway and with the BRAF mutation status. However, based on the current data and information available, no recommendation can be given over the sequencing of therapies.

The safety and tolerability of the combination therapy appears to be manageable and there were no new unexpected ADRs observed in the safety database during the conduct of the two pivotal studies.

4. Recommendations

Outcome

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

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

Extension of indication to add a new therapeutic indication for the use in combination of trametinib and dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see sections 4.4 and 5.1).
As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly. An updated RMP was also provided.

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

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The PRAC considers that no additional risk minimisation measures will be necessary for the safe and effective use of the medicinal products. The CHMP endorsed this advice.

- **Obligation to conduct post-authorisation measures**

No conditions are necessary.

Market exclusivity

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication for both Mekinist and Tafinlar brings significant clinical benefit in comparison with existing therapies (see appendix 1).

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 add a new therapeutic indication for the use in combination of trametinib and dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see sections 4.4 and 5.1). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.3 of the SmPC are updated. The Package Leaflet was updated accordingly. Furthermore, an updated Mekinist (trametinib) RMP version 11.1 and Tafinlar (dabrafenib) RMP version 7.1 was approved as part of the application.

Summary

Please refer to the Scientific Discussion Mekinist-Tafinlar-WS-0736.