25 April 2014
EMA/CHMP/258608/2014
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Mekinist

International non-proprietary name: trametinib

Procedure No.: EMEA/H/C/002643/0000

Note

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

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Product information

Name of the medicinal product:	Mekinist
Applicant:	Glaxo Group Ltd 980 Great West Road Brentford Middlesex TW8 9GS UNITED KINGDOM
Active substance:	trametinib
International Non-proprietary Name/Common Name:	trametinib
Pharmaco-therapeutic group (ATC Code):	(L01XE25)
Therapeutic indication:	Trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Trametinib has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy (see section 5.1).
Pharmaceutical form:	Film-coated tablet
Strengths:	0.5 mg, 1 mg and 2 mg
Route of administration:	Oral use
Packaging:	bottle (HDPE)
Package sizes:	30 tablets and 7 tablets

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List of abbreviations

AE	Adverse Event
AESI	Adverse event of special interest
ADME	Absorption, Distribution, Metabolism and Excretion
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under concentration-time curve
AUC_{inf}	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC_{0-t}	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration
$AUC_{0-\tau}$	Area under the concentration-time curve over the dosing interval
BCRP	Breast cancer resistance protein
BID	Twice daily
C_{avg}	Average concentration
CI	Confidence Interval
CL	Systemic clearance of parent drug
CL/F	Oral clearance
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
$C_{min, obs}$	Observed pre-dose concentration
$C_{min, pred}$	Predicted pre-dose concentration
CPH	Cox Proportional Hazard
CR	Complete response
CSR	Central Serous retinopathy
C_{τ}	Pre-dose (trough) concentration at the end of the dosing interval
C_t	Last observed quantifiable concentration
cuSCC	Cutaneous squamous cell carcinoma
CV	Coefficient of variability
CYP	Cytochrome

DDI	Drug-drug interaction(s)
DISS	Dabrafenib Integrated Summary of Safety
DRM	Drug-related material
DTIC	Dacarbazine
ECOG	EasternCooperative Oncology Group
F	Absolute bioavailability
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FTIH	First time in humans
GFR	Glomerular filtration rate
GLS	Geometric Least-Squares
GSK1120212	trametinib
GSK1790627	trametinib metabolite M5
GSK2118436	dabrafenib
GSK2298683	dabrafenib metabolite M4
GSK2285403	dabrafenib metabolite M7
GSK2167542	dabrafenib metabolite M8
h	Hour(s)
HR	Hazard ratio
IC_{50}	Concentration causing 50% inhibition
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IV	Intravenous
KD	Rate constant describing tumour shrinkage
kg	Kilogram
λ	Rate constant describing rate of resistance/progression
L or l	Liter
LD	Loading dose
LDH	Lactate dehydrogenase
LLN	Lower limit of normal

LLQ	Lower limit of quantification
LVEF	Left ventricular ejection fraction
m^2	Meter squared
max	Maximum
MC	Multi-centre
MEK	Mitogen-activated extracellular signal regulated kinase
mg	Milligram
min	Minimum or minute
mL	Milliliter
msec	Milliseconds
MTD	Maximum tolerated dose
NA	Not available/assessed
NCI	National Cancer Institute
ND	Not done
ng	Nanogram
NSAIDs	Non-Steroidal Inflammatory Drugs
NSCLC	Non-small cell lung cancer
OATP	Organic anion transporting polypeptide
OD	Once daily
ORR	Overall Response Rate
OS	Overall Survival
PACDP	Pooled Any Combination Dose Population
PD	Pharmacodynamic
pERK	Phosphorylated ERK
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic
QTc	Corrected QT interval
QTcF	QT duration corrected for heart rate by Fredericia's formula
QTcP	QT duration corrected using estimated population factor

RBC	Red blood cells
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SD	Standard deviation or Single dose
t	Time of last observed quantifiable concentration
$t_{1/2}$	Terminal phase half-life
$t_{1/2, eff}$	Effective terminal phase half-life
τ	Dosing interval
t_{max}	Time of occurrence of C_{max}
TS	Tumour Size
ULN	Upper limit of normal
uTISS	Updated Trametinib Integrated Summary of Safety
Vd	Volume of distribution
Vc/F	Apparent central volume of distribution following oral dosing
Vp/F	Apparent peripheral volume of distribution following oral dosing
pcVPCs	Visual Predictive Checks

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Glaxo Group Ltd submitted on 7 February 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Mekinist, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 September 2011.

The applicant applied for the following indication: Trametinib in combination with dabrafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Trametinib monotherapy is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Trametinib monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy (see section 5.1).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that trametinib was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decisions P/0044/2012, P/345/2010 on the agreement of a paediatric investigation plan (PIP) and on the granting of a class waiver.

At the time of submission of the application, the PIP P/0044/2012 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Applicant's request for consideration

New active Substance status

The applicant requested the active substance trametinib contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union

Scientific Advice

The applicant received Scientific Advice from the CHMP on 21 October 2010 and 14 April 2011. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

Mekinist has been given a Marketing Authorisation in the USA on 29 May 2013 and in Canada on 18 July 2013.

A new application was filed in the following countries: Australia, Switzerland, Turkey, Israel and Russia.

1.2. Manufacturers

Manufacturer responsible for batch release

Glaxo Wellcome, S.A.

Avda. Extremadura, 3

09400, Aranda de Duero

Burgos

Spain

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pieter de Graeff	Co-Rapporteur:	Filip Josephson

CHMP Peer reviewer: Alar Irs

- The application was received by the EMA on 7 February 2013.
- The procedure started on 27 February 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 May 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 17 May 2013.
- PRAC RMP advice and assessment overview adopted by PRAC on 16 June 2013.
- During the meeting on 27 June 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 28 June 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 September 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 October 2013.

- During the CHMP meeting on 21 November 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- PRAC RMP advice and assessment overview adopted by PRAC on 7 November 2013.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 January 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 February 2014.
- PRAC RMP advice and assessment overview adopted by PRAC on 6 March 2014.
- During the CHMP meeting on 18 March 2014, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 25 April 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Mekinist.

2. Scientific discussion

2.1. Introduction

Problem statement

Cutaneous melanoma is the most aggressive form of skin cancers. Each year approximately 130,000 people are diagnosed with melanoma worldwide. Despite improving surveillance and treatment techniques it is estimated that annually 30,000 people die because of the disease. Death rate in Europe is estimated to be 3.9 persons per 100.000. According to the program for Surveillance Epidemiology and End Results (SEER) of the National Cancer Institute between 2001 and 2007, 8% of patients were first diagnosed with stage III (regional metastasis) melanoma and 4% of patients with stage IV (distant metastasis) disease.

The vast majority of melanoma patients with early stage localized disease are cured with (repeated) surgery alone. However those with unresectable or metastatic melanoma have a poor prognosis. Dacarbazine has been used since the seventies in Europe as first line treatment of metastatic melanoma, despite the low response rate (below 20%), the short duration of response, and the absence of any survival advantage[1].

In 2011 the treatment options for metastatic melanoma expanded with the introduction of the anti CTLA4 directed ipilimumab (Yervoy) and the BRAF inhibitor vemurafenib (Zelboraf); dabrafenib (Tafinlar) was subsequently approved.

[1] Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364:2507-16.

Ipilimumab based on the results of a phase III study performed in previously treated melanoma patients was associated with a statistically significant improvement in overall survival (OS) compared with the gp100 vaccine (10.1 months versus 6.4 months; HR: 0.66; p= 0.003). Vemurafenib (Zelboraf), as first line treatment of patients with unresectable locally advanced or metastatic melanoma harbouring BRAF V600 mutations based on the results of the pivotal phase III study (BRIM3) was associated with a statistically significant improvement in progression-free survival (PFS) (HR 0.38, 95%CI: 0.32-0.46, p<0.0001, median PFS 6.9 vs 1.6 months, respectively) and in OS (HR 0.70, 95%CI: 0.57-0.87, p<0.0001, median OS 13.6 vs 9.7 months, respectively), compared with DTIC.

Specific mutations of the BRAF-oncogene (especially V600E, and less frequently V600K, V600D, V600R) are identified in approximately 40-50% of cutaneous melanomas (Colombino et al., 2012).

Dabrafenib (Tafinlar) based on the results of the pivotal phase III BREAK study was associated with a statistically significant improvement in PFS (HR 0.30, 95%CI: 0.18-0.53, p<0.0001, median PFS 5.1 vs 2.7 months, respectively) and in the updated analysis with a trend in OS (HR=0.76, 95% CI: 0.48-1.21, median OS 18.2 vs. 15.6 months, respectively), compared with DTIC.

Despite the recent innovations the prognosis of patients with unresectable or metastatic melanoma remains poor and patients with melanoma stage IIIc or IV disease still face median overall survival of approximately one year. There is clearly an unmet medical need for this population.

About the product

- Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors.

- ATC code: L01XE25 trametinib (assigned but not formally approved by the WHO International Working Group for Drug Statistics Methodology).

Trametinib (GSK1120212) is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. MEK1 and MEK2 are proteins in the central signal transduction pathway and are critical for cell proliferation and survival. Trametinib has been developed specifically to address known oncogenic mutations in upstream MAPK pathway proteins BRAF and Ras, which signal through MEK1 and MEK2. The pharmaceutical form and strength are 0.5 mg, 1 mg or 2 mg film-coated tablets.

The recommended dose of trametinibis 2 mg given orally once daily (QD).

Development programme/compliance with CHMP guidance/scientific advice

Scientific advice

Scientific advice from the CHMP was sought for both the use of trametinib as monotherapy and in combination with dabrafenib, for the treatment of unresectable or metastatic melanoma with BRAF V600 mutations. Advice was provided by the Scientific Advice Working Party (SAWP) of the Committee for Medicinal Products for Human Use (CHMP) in 2010 (EMA/CHMP/SWAP/620177/2010). A co-primary endpoint of OS and PFS for the pivotal study to be conducted with trametinib was proposed by the Applicant, but the CHMP considered that PFS as primary endpoint would have been sufficiently informative to enable a proper benefit-risk assessment, in view of the potential confounding effect of next line therapies and the possible necessity to allow cross-over in order to make the study feasible from an ethics committees and patient/investigator's perspective.

For the development of the combination treatment of trametinib with dabrafenib a SA was requested in February 2011 (EMA/CHMP/SAWP/261249/2011). OS as primary endpoint was considered acceptable, however a concern was raised regarding the potential confounding effect of ipilimumab after progression. Testing PFS followed by OS assessment was suggested as an alternative strategy. In the advice it was also suggested to consider planning for a protocol-defined comparison of the BRAF inhibitor/MEK inhibitor combination vs. sequential administration of MEKi-BRAF-i, comparing PFS-1- on the combination regimen with PFS-2- on a sequential regimen.

Paediatric Investigation Plan

A Paediatric investigation plan for treatment of melanoma and of solid malignant tumours other than melanoma had been agreed. For melanoma, a deferral was granted for studies in patients from 12 to less than 18 years of age, and studies in patients from birth to less than 12 years were waived. For solid malignant tumours other than melanoma, a deferral was granted for studies in patients from 28 days to less than 18 years of age, and studies in patients from birth to less than 28 days of age were waived. The paediatric investigation plan should be completed by October 2019.

General comments on compliance with GCP

All clinical studies were conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained for all subjects, and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted.

Type of application and other comments on the submitted dossier

Legal basis

The application for marketing authorisation through the centralised procedure for Mekinist (trametinib) film-coated tablets was submitted according to Article 8.3 of Directive 2001/83/EC. The application is a complete and independent application, for a new active substance.

The Applicant requested an accelerated assessment before submission of the application which was agreed by the CHMP. However the timetable was reverted to a normal timeframe at the time of adoption of the day 120 list of questions.

The Applicant requested with the Day 121 responses consideration of a conditional marketing authorisation approval. The results of the ongoing phase III confirmatory trial exploring activity of dabrafenib in combination with trametinib in the proposed target population are expected in late 2013, and could be assessed within the timeframe of this procedure, the request for conditional marketing authorisation was therefore not endorsed by the CHMP.

The applicant requested the approval for the following indications:

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

Trametinib monotherapy is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Trametinib monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy (see section 5.1).

The final indication following CHMP review of this application is:

Trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Trametinib has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy (see section 5.1).

2.2. Quality aspects

2.2.1. Introduction

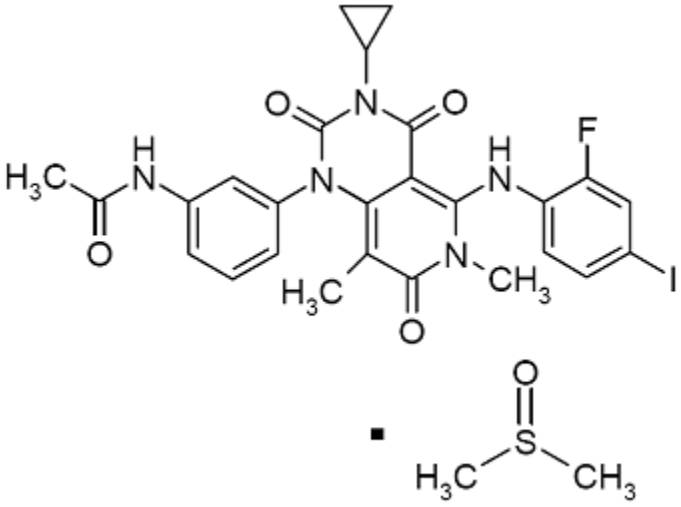
Mekinist is presented as film-coated tablets containing 0.5 mg, 1 mg and 2 mg of trametinib as active substance.

Other ingredients are: mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate, sodium laurilsulfate, colloidal silicon dioxide, titanium dioxide, polyethylene glycol, iron oxide yellow (0.5 mg tablets), polysorbate 80, and iron oxide red (2 mg tablets).

The product is available in high-density polyethylene (HDPE) bottle with child resistant polypropylene closure. The bottle contains a desiccant.

2.2.2. Active Substance

The chemical name of trametinib is equimolecular combination of *N*-(3-{3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2H)-yl}phenyl)acetamide with (methylsulfinyl)methane and has the following structure:



Trametinib dimethyl sulfoxide is a 1:1 stoichiometric DMSO solvate, where DMSO is fully incorporated into the crystal lattice. In solid state one form has been identified (form 1), and it has been consistently produced by the synthetic process used in development and is the proposed commercial solid state form. The active substance is a white to almost white solid, very slightly soluble in ethanol (non-solvated parent) and acetonitrile and slightly soluble in DMSO (solvated) and isopropyl acetate. In the different pH the substance is very slightly soluble (up to 24 hours). Chiral centers are not present in this active substance. It was noted that micronised trametinib dimethyl sulfoxide form 1 adsorbs approximately 0.3% w/w water between 0% and 90% relative humidity at 25 °C.

Confirmation of the chemical structure of trametinib dimethyl sulfoxide is provided by single crystal X-ray crystallography and by spectroscopic analysis (^{1}H NMR and ^{13}C NMR, MS and IR,)

Manufacture

Trametinib dimethyl sulphoxide is manufactured in a seven step process and purified by crystallisation. The product is micronized in the final part of the process. The process is described in sufficient detail concerning raw materials used, process conditions and controls. The designation of the starting materials for the synthesis of the active substance has been justified with respect to their impurity profiles, their potential for a carry-over into the final active substance, their structural complexity and with respect to their proximity to the final intermediate and the active substance, respectively.

The active substance has been developed using a Quality by Design (QbD) approach, in line with ICH Q8, Q9, Q10, Q11 and other regulatory guidance. However, no Design Space was proposed.

The critical process parameters (CPP) and their ranges have been clearly highlighted in line with the development data. Amounts to be used for the different materials are indicated in ranges . Details on the mixture time, temperatures, etc. are provided in relation to the critical parts of the process (CPPs).

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterisation. The discussion on the genotoxic impurities is sufficiently detailed and it is considered acceptable. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

The active substance specifications have been established in-house. The proposed specifications are acceptable in view of the route of synthesis and the various European guidelines.

The active substance specification includes tests for appearance (visual), identity (IR), solid state (XRPD), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), particle size (laser diffraction).

The discussion on the genotoxic impurities is considered as sufficient. The analytical methods are adequately described and validated.

Batch analysis data are given for three production scale batches and 13 batches used for the safety and clinical studies. The results are within the specifications and consistent from batch to batch.

Stability

Stability data are presented for three commercial scale batches of trametinib. The batches were stored in double low-density PE bag inside with desiccant in between and place in a aluminium foil laminated pouch. Comparative batch analysis data demonstrate that batches manufactured via the commercial process and micronized at the proposed commercial site are chemically and physically comparable to the trametinib dimethyl sulfoxide used in the Phase 3 clinical and primary stability studies.

The results of long-term and accelerated stability studies demonstrate the chemical and physical stability of trametinib dimethyl sulfoxide when stored for up to 36 months at 30°C/65%RH, or for up to 6 months at 40°C/75%RH. The analytical methods used were the same as for release and were stability indicating. No significant changes were observed in the parameters tested (description, trametinib dimethyl sulfoxide content, drug-related impurities content, DMSO content, water content, solid state form or particle size). All results complied with specification.

In addition, data were presented following short-term storage of the active substance under stress conditions. All three primary stability batches were stored at 50°C/ambient humidity for 3 months. No significant changes were observed in any of the parameters, all results complied with the specification.

Forced degradation studies of trametinib dimethyl sulfoxide have also been performed. In the solid state include 80 °C for 14 days, 80 °C/75% RH for 14 days and ICHQ1B option 1. Solution phase studies include acid (0.1 M HCl) 60 °C, 4h; base 0.1 M NaOH 25 °C, 1 h and oxidation by air headspace with N-Methyl pyrrolidone. The acid and base conditions required the addition of acetonitrile to enhance the solubility of trametinib dimethyl sulfoxide. GSK1790627A and GSK1732244A were identified as the major degradation products under acidic and oxidative conditions, respectively. These impurities are also synthetic impurities controlled by the active substance specification. Trametinib was chemically stable in the solid state under all stressing conditions used in the forced degradation study. No evidence of significant levels of degradation products was observed.

One primary stability batch was exposed to light, within the proposed package, in accordance with ICH Q1B. Only two degradation products were formed after exposure to light, with the total of degradation products detected being less than 0.5% area. None of the degradation products reported increased above the identification threshold (>0.10%) specified in ICH Q3A. The active substance is not sensitive to light.

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

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The product has been developed using a Quality by Design (QbD) approach, in line with ICH Q8, Q9, Q10, Q11 and other regulatory guidance. It was noted that no Design Space has been proposed by the Applicant.

The Quality Target Product Profile (QTPP) for trametinib tablets was to provide an immediate release oral dosage form with adequate stability and flexible dosing using a wide range of dosage strengths from 0.125 mg to 20 mg as trametinib. The range of dosage strengths was later narrowed to 0.5 mg to 2 mg based on the maximum tolerated dose of 3 mg/day. Special consideration was given to the size of the tablets in order to facilitate swallowing.

Design selection of the drug product formulation and manufacturing process reflects the QTPP, the characteristics of the input materials (active substance and excipients), prior knowledge, and product specific understanding based on development history. Design selection included the dosage form, strengths, appearance of the tablets, particle size distribution of the active substance substance, and the choice of a manufacturing process and packaging minimising exposure to humidity in order to limit desolvation (loss of DMSO). A dry blending process and coating with relatively high evaporation rate conditions were chosen.

Excipients were selected based on their compatibility with the active substance, manufacturability, and impact on performance of the finished product. Due to the intended small tablet size for all strength, a common blend approach was not possible. With the exception of the coating of the 0.5 mg strength, the formulation of the tablets remained unchanged throughout development. The coating of the 0.5 mg strength was changed from opadry white to opadry yellow in order to improve photostability.

Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) have been identified, and a control strategy has been developed to ensure product quality.

The finished product CQAs are description, identification, trametinib content, DMSO content, drug-related impurities content, uniformity of dosage units, and dissolution. In addition, the coated tablets are tested for water content at release. The parameters and attributes contributing to finished product CQA variability have been established and controls have been defined to ensure that the performance criteria are consistently and reliably met.

Risk assessments, using structured methodologies such as Failure Mode and Effects Analysis (FMEA), in accordance with ICH Q9, were used to establish those process parameters and attributes that are likely to have the greatest impact on product quality.

Control strategies were developed for the three stages of the manufacturing process.

Following the start of commercial manufacture, ongoing monitoring, trending and review will be conducted to provide confidence that the control strategy will ensure product quality. Risk management, together with any continuous improvement opportunities, will be applied throughout the product lifecycle to maintain the control strategy to meet product quality requirements.

Except for the commercially available coating materials, all excipients are of pharmacopoeial grade. There are no novel excipients used in the finished product formulation. Acceptable in-house specifications were provided for the commercially available coating materials. The list of excipients is included in section 6.1 of the SmPC.

Trametinib tablets, 0.5 mg, 1 mg, 2 mg are packed with silica gel desiccant into opaque, white high density polyethylene (HDPE) bottles, and closed with polypropylene screw closures, with a polyethylene-faced foil induction heat-seal liner. The HDPE is pigmented white with titanium dioxide. The container closure system was chosen because low tablet moisture content was desirable due to the loss of DMSO solvent in the presence of moisture. The presence of silica gel is essential to maintain a low moisture atmosphere during the entire shelf life. The primary packaging is described as stated in the SmPC and complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacturing process includes blending, compression, film-coating and packaging. A flow diagram and a description of the manufacturing process were provided identifying all critical process parameters (CPPs), critical quality attributes (CQAs), as well as attributes which serve as in-process controls. The finished product is controlled according to an in-house specification.

All batches manufactured using the process described have produced finished product of acceptable quality and performance showing that this product can be manufactured reproducibly according to the agreed finished product specification, which is suitable for the control of this oral preparation.

Due to the low drug load (<2%), the finished product is regarded as non-standard dosage form. The Applicant applies a three-stage lifecycle approach for process validation. During the second stage, the manufacturing process was successfully evaluated at the commercial site with three commercial scale batches of each strength supported by two clinical batches of the 0.5 mg and 2 mg strengths.

The description of the manufacturing process and the proposed in process controls are consistent with the manufacturing process development data and the proposed control strategy. PARs were indicated for CPP and non-CPP.

For critical and non-critical process parameters/attributes ranges, future changes to the defined PARs will be managed under the site's Pharmaceutical Quality System with regulatory action in conformance with post-approval regulations and guidance.

The proposed batch size is acceptable in view of the provided process evaluation data which were obtained at this scale.

Product specification

The control of finished product quality is done via in-house specifications. The product specification includes tests for description (visual), identification of trametinib (HPLC-UV), trametinib content (HPLC), uniformity of dosage units (HPLC), drug-related impurities (HPLC), DMSO content (HPLC), water content (KF), dissolution (HPLC), and microbial enumeration tests (Ph Eur). The release and shelf life specifications differ with regard to DMSO content.

The analytical methods were adequately described and validated. Batch analytical data were presented for three commercial image batches of each strength produced by the proposed commercial manufacturing process, as well as batch analysis data of clinical batches, demonstrating compliance with the release specification and confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

The conditions used in the stability studies are according to the ICH stability guideline. All batches were manufactured at the proposed commercial manufacturing site. The batches were stored in HDPE bottles with desiccant.

The primary stability data include three commercial scale batches of each strength stored at 5°C/ambient humidity (24 months, one batch per strength), 25°C/60% RH (24 months) and 40°C/75% RH (six months). Significant changes were observed for DMSO content at 40°C/75% RH and decreasing trends were observed at the other storage conditions. Increasing trends were seen for water content. DMSO desolvation appeared to be dependent on temperature and moisture. As a consequence, storage in the refrigerator was evaluated as long term storage condition.

Photostability of one batch of each strength was studied under ICH Q1B conditions. Tablets of the 0.5 mg strength were not photostable when directly exposed to light or in the primary packaging. Tablets of the 1 mg strength were photostable in the primary packaging. Tablets of the 2 mg strength were photostable when directly exposed.

Due to a change in coating of the tablets of the 0.5 mg strength in view of the insufficient photostability in the primary package, a change in the dimensions of the tablets of the 2 mg strength during development of the manufacturing process, and the observed DMSO desolvation, additional stability data were generated for three commercial scale batches of each strength stored at 5°C/ambient humidity (0.5 mg and 2 strengths: 12 – 18 months, 1 mg strength: six months), 25°C/60% RH (0.5 mg and 2 strengths: 12 – 18 months, 1 mg strength: six months) and 40°C/75% RH (six months). No significant change was observed at 5°C/ambient humidity. Significant changes in DMSO content were observed after 24 months at 25°C/60% RH, however, specifications were met when tested after 18 months of storage. All batches failed to meet the proposed DMSO content limit after six months at 40°C/75% RH. Statistical evaluation of the DMSO content data obtained at 5°C support a shelf life of at least 23 months.

Tablets of the 0.5 mg strength with the adapted coating were photostable in the primary packaging while the tablets of the 2 mg strength with the adapted dimensions were photostable when directly exposed.

In use stability studies showed that the product can be stored by patients at temperatures up to 30°C for 30 days. Refrigerated storage for unopened bottles is applicable for the supply chain and for patients.

Based on the provided stability data, the proposed shelf life of 18 months and storage conditions “Store in a refrigerator (2° to 8°C)” are justified. Once opened, the bottle may be stored for 30 days at not more than 30°C. The tablets should be kept in the bottle tightly closed to protect from light and moisture.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality of Mekinist is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorisation. The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product. Proven Acceptable Ranges were indicated for Critical Process Parameters and non-Critical Process Parameters.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

The primary and secondary pharmacodynamics of trametinib were investigated in a number of in vitro and in vivo studies.

Trametinib was tested in rats and dogs by oral gavage for the toxicology studies. In addition, safety pharmacology studies were carried out in rats (oral administration), in rabbit (oral administration), and in dogs (oral and iv administration over 10 minutes). Pivotal toxicology studies and most of the safety pharmacology studies were carried-out in compliance with GLP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

A series of in vitro and in vivo investigations have been conducted in order to characterise the primary pharmacology of trametinib with respect to the treatment of advanced cancer. It was shown that trametinib is a selective inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. It inhibits MEK1 and 2 phosphorylation as well as the phosphorylation of ERK1 and 2 thereby inducing INK4B (p15) protein (an endogenous cyclin dependent kinase [CDK] inhibitor). Following a screening of kinases, it was shown that trametinib preferentially inhibits BRAFV600E-mediated MEK1 activation (IC50 = 0.7 nM) over phospho-MEK1 activity (IC50 = 13 nM) and MEK2 activation (IC50 = 0.9 nM) over phospho-MEK2 activity (IC50 = 11 nM).

Eighty (80) % of BRAF and 72% of RAS mutant cell lines were sensitive to trametinib. The minimum concentration of trametinib required to induce growth inhibition in highly sensitive BRAF mutant melanoma cell lines was >10.4 ng/mL (~15 nM). Trametinib caused G0/G1 arrest in HT-29 and Colo205 cells by inhibiting ERK phosphorylation, resulting in quantitative and qualitative changes in cell cycle proteins downstream and subsequently induced apoptosis.

Furthermore, the anti-proliferative properties of trametinib were shown in other human cell lines of haematological origin. However, trametinib generally showed poor to no activity against B-cell leukemia, B-cell lymphoma and Burkitt's lymphoma.

Trametinib was studied in combination with other anticancer drugs to determine the combinatorial effect on cell growth inhibition in a variety of cancer cell lines. Results showed that trametinib had mostly synergistic effects when combined with dabrafenib or a PI3K/mTOR inhibitor in BRAF mutant melanoma cell lines. However, twenty-four hours after treatment, the combination of trametinib with dabrafenib did not increase apoptosis more than either single agent alone in the eight BRAFV600E/K melanoma cell lines tested (data not shown).

Biochemical and cellular activities of trametinib and the metabolite M5 (produced by deacetylation of trametinib) showed that both compounds were similarly active to inhibit BRAFV600E-mediated MEK1 activation, phospho-MEK1 activity, cellular phosphorylation of ERK and cellular proliferation of BRAFV600E mutant SK-MEL-28 cells. A second metabolite known as M7 (formed by mono-oxygenation of M5) inhibited the activated human MEK1 enzyme with approximately 10-fold less potency than trametinib having an IC50 value of 73 ± 4 nM compared to 7.0 ± 0.1 nM. Both most important metabolites occur in human plasma in about 10% of the total of trametinib and related compounds.

Chronic administration in human tumour xenograft models in mice showed that trametinib was an orally efficacious MEK1 and MEK2 inhibitor causing inhibition of ERK phosphorylation, and accumulation of p27 and reduction of Ki67, both markers of cell cycle arrest. It significantly inhibited the growth of melanoma xenografts by 82% after 21 days of dosing at 0.3 mg/kg.

The anti-tumour efficacy of trametinib alone or in combination with the BRAF inhibitor dabrafenib was evaluated in A375PF11 BRAFV600E human melanoma mouse xenografts. The combination of trametinib with dabrafenib was well tolerated and resulted in delayed tumour resistance and significant survival improvement. Combination studies with extended dosing showed prolonged tumour growth inhibition and delayed tumour outgrowth when compared to treatment with the single agents. Sequential administration of one week dabrafenib (30 mg/kg) and the other week trametinib (3 mg/kg) for 11 weeks showed the best results in reduction of tumour volume.

Secondary pharmacodynamic studies

Trametinib, as the parent compound or the DMSO solvate, was evaluated in a total of 50 kinase assays covering 44 unique kinase enzymes. Trametinib was inactive (IC50 >10 μM) against all but the B-Raf^{V600E} MEK1 cascade assay (BRAMA). This assay monitors the ATPase activity of phosphorylated-MEK1 that results from the phosphorylation of MEK by BRAF^{V600E}. The IC50 of 63 nM for trametinib was due to inhibition of MEK activation rather than the direct inhibition of BRAF^{V600E}. Trametinib was also evaluated against 171 different kinase assays using an external kinase screening panel which found no significant (>50%) inhibition was observed when screened at a single concentration of 10 μM. In a separate study, trametinib was examined for effects in 7 enzyme assays (phospholipase A2, cyclooxygenase isoform 1 [COX1], constitutive NO synthase [NOS], phosphodiesterase 4, protein kinase C, acetylcholinesterase, monoamine oxidase A). Trametinib at a fixed concentration of 10 μM showed no significant inhibitory effect on these enzymes.

Safety pharmacology

At the relevant low dose of 3 mg/kg, tolerated by rats and dogs, with the exception of diarrhoea and inhibition of body weight gain, no significant effects on general behaviour, physiologic function or acute neurotoxicity were observed. However, administration of trametinib to rats at the high dose of 100mg/kg (non GLP) resulted in decreased body weight gain, sporadic incidence of reduced spontaneous locomotion, prone position, blepharoptosis, diarrhoea, piloerection and mydriasis, described in order of onset. Subsequent studies showed that this dose leads to morbidity and mortality.

Following increasing oral doses of trametinib it was shown that it had no effect on the respiratory system of rats up to a dose of 0.125 mg/kg in which case it produced a mild, transient decrease in body temperature (up to 0.8°C) at 1 hour post dose.

In a preliminary, in vitro screening assay, trametinib was found to inhibit hERG channel tail current in a concentration-dependent manner. In an in vitro rabbit preparation it was shown that trametinib produced significant decreases in isometric contractile force and the Tp-e interval at high concentrations. In a GLP study done on dogs with increasing oral doses, trametinib had no effect on ECG parameters, blood pressure or heart rate.

Pharmacokinetics

The pharmacokinetics, distribution, metabolism and elimination of trametinib have been investigated in a series of oral or intravenous in vivo studies in the mouse, rat, dog, monkey and human, and in in vitro studies, using non-radiolabelled and 14C-labelled drug.

Absorption

Trametinib was absorbed slowly after oral dosing in the rat (Tmax 4-8 h), whereas peak plasma concentrations were reached 1-2 h post-dose in mouse and monkey and 3 h in dog. Oral bioavailability following administration of trametinib acetic acid solvate differed between species: 111% in mice, 48% in rats, 86% in dogs and 49% in monkeys. After iv administration, trametinib showed a moderate to low plasma clearance in all species examined. The half-live values were long, 3.7 h for mouse, 6.1 h for rat, 6.7 h for monkey and 14.5 h for dog.

Distribution

Drug-related radioactivity distributed into most tissues within 2 hours after oral administration. Highest tissue concentrations were measured in liver, kidney, renal cortex, Harderian gland, pancreas, salivary glands and adrenal cortex. Trametinib-related radioactivity was also distributed into the brain, although to a limited extent (brain-blood ratio: 0.1-0.6). Seven days after the single dose, drug-related radioactivity was still observed in spleen, kidney, liver and preputial gland, suggesting potential accumulation of trametinib-related material in these organs when administered daily. No selective association of trametinib-related radioactivity with melanin-containing tissues was observed. Studies on placental transfer of trametinib were not performed.

Plasma protein binding

The in vitro plasma protein binding of trametinib at high (0.5-5 µg/mL) and clinically relevant concentrations (0.001-0.05 µg/mL) was high in all species: 95% in mouse and 96% in rat, 97% in dog, 98% in monkey and 97% in human and no concentration dependency was observed.

Partitioning of trametinib into red blood cells was low (blood-to-plasma ratio <0.9) in any of the species investigated in in vitro studies. Comparable partitioning was observed in in vivo studies at early time points post-dose, while a higher partitioning was observed at later time points post-dose (blood-to-plasma ratio 2-3). At clinically relevant concentrations, trametinib-related radioactivity was distributed preferably into blood cells by a factor 3 to 8.

Metabolism

Three metabolites of trametinib were identified in in vitro studies: M5, M6 and M7. These metabolites were all products of deacetylation, which is the predominant pathway in trametinib elimination. M7 was formed by deactetylation and oxidation, and CYP3A4 may be involved in the oxidative metabolism of trametinib. The major in vitro metabolites of trametinib observed in humans were also detected in the nonclinical species.

The major circulating component in rats and dogs was unchanged trametinib, accounting for 64-94% and 58-79% of total plasma radioactivity, respectively. A similar pattern was observed in humans. In both rats and dogs, the two Phase I metabolites M5 and M7 were detected in plasma at levels of <6% and 9% of drug-related material, respectively, while M6 (N-glucuronidation of M5) was detected in rat bile and accounted for <12% of the dose. M5 is a pharmacologically active metabolite. A study regarding the plasma protein binding of M5 is still ongoing but preliminary data indicate that the free fraction of M5 is 1.2%.

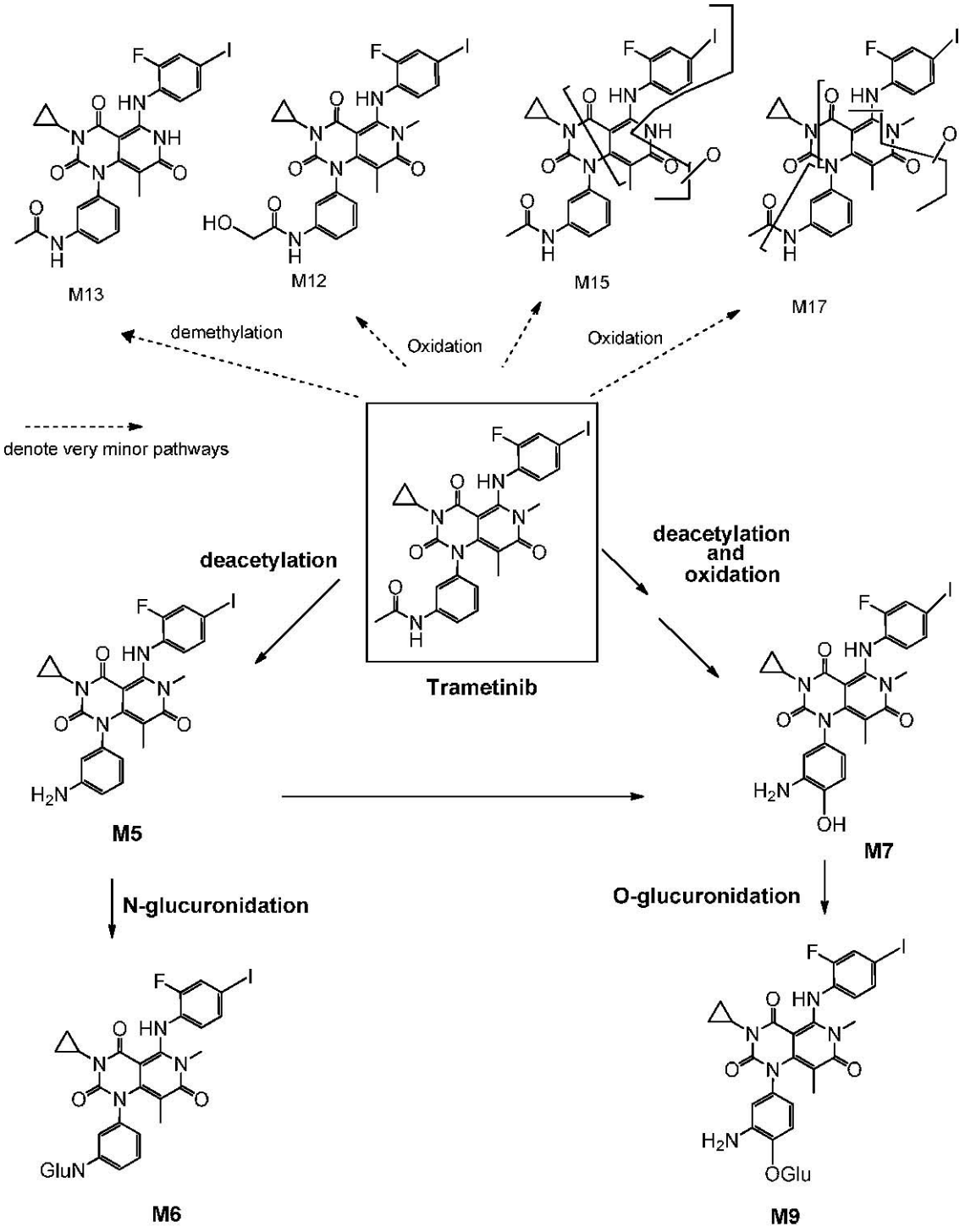


Figure 1: Trametinib Extended Metabolism Scheme

Excretion

The predominant route of elimination of drug-related radioactivity was via faeces in rats and dogs (59-98%). Most of the radioactivity was recovered in excreta within 3 days in rats and dogs. However, small amounts of radioactivity continued to be eliminated until 7 days, indicating protracted elimination consistent with the long half-lives.

Metabolites M5 and M7 were observed in rat excreta, while only M7 was detected in dog excreta. As they were co-eluted with a number of other minor metabolites, exact levels of each could not be quantified.

Metabolites in human excreta included M5, M7 and M9 (O-glucuronidation of M7) although M9 was only observed as a minor component in urine.

Pharmacokinetic drug interactions

The substrate characteristics of trametinib were investigated for P-gp and BCRP, and in vitro inhibition has been investigated for P-gp, BCRP, OATP1B1 and OATP1B3. In vitro data showed that trametinib is an inhibitor of both human OATP1B1 and OATP1B3 P-gp BCRP. In addition, it was shown that trametinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6 and CYP3A4. Trametinib was found to be an in vitro inhibitor of CYP2C8, CYP2C9 and CYP2C19 and an inducer of CYP3A4. Trametinib is not a substrate of CYP enzymes.

2.3.3. Toxicology

Single dose toxicity

Table 1: Single dose toxicity studies with trametinib

Study ID	Species/ Sex/Number/ Group	Dose/Route mg/kg	Approx. lethal dose / observed max non-lethal dose	Major findings
CD2008/00117/00 (JTP74057-TX-001)	Rat 3M	Oral gavage dose escalation 3, 10, 30, 100	>100 / 100	≥ 3: bw loss ≥ 10: macroscopic lesions in liver
CD2006/00919/01 (D06241)	Beagle dog 1/sex/group	Oral gavage dose escalation 0.15, 0.5, 3	3 / 0.5	≤ 0.5: reticulocytes↓, Hb↓ ≥ 0.5: WBC↑, ALP↑, P↑ 3: bw loss, activity↓, dehydration, soft feces, GI damage, lymphoid organ depletion, bone marrow cellularity↓, labored breathing, killed in moribund condition, F: red blood cell parameters ↑

bw=body weight; M=male; F=female; GI=gastrointestinal; Hb=haemoglobin; WBC=white blood cells; P=serum inorganic phosphorus; ALP=alkaline phosphatase

Repeat dose toxicity

Table 2: Repeat-dose toxicity studies with trametinib

Study ID	Species/Sex/ Number/Group	Dose/Route mg/kg/day	Duration	NOEL/ NOAEL mg/kg/ day	Major findings
Pivotal studies					
CD2007/00984/ 00 (G07042)	Rat 10/sex/group + 6/sex/group recovery + 3/sex/group TK	Oral gavage 0, 0.016, 0.031, 0.0625, 0.125	3 weeks + 2 weeks recovery	< 0.016	**≥ 0.016**: liver vacuolation, M: ret↓, eos↓, F: neut↑, mono↑, stomach min **≥ 0.031**: M: blood urea↑ **≥ 0.0625**: skin lesions, P↑, ALT↑, AST↑ **0.125**: mortality (1F), albumin↓, M: neut↑, F: RBC parameters↓, ret↑, platelets↑, blood urea↑, urine protein↑, bone marrow myeloid hyperplasia, lymph nodes increased cellularity, liver necrosis
CD2010/00178/ 00 (G09108)	Rat 12/sex/group + 6/sex/group recovery + 3/sex/group TK	Oral gavage M: 0, 0.031, 0.0625, 0.125 F: 0, 0.016, 0.031, 0.0625	13 weeks + 4 weeks recovery	M: NOEL 0.016 F: < 0.016	**≥ 0.016**: F: ovary cyst, corpora lutea↓ **≥ 0.031**: lymph↓, skin lesions, stomach min+erosion + hyperplasia squamous mucosa + inflammation, F: albumin↓, bone marrow myeloid hypercell., liver vacuolation, lymph node hyperplasia **≥ 0.0625**: mortality (3M, 4F), RBC parameters↓, neut↑, P↑, adrenal cortex hyperplasia, M: albumin↓, bone marrow necrosis+ myeloid hypercell.,liver vacuolation, lymph node hyperplasia, lung hemorrhage, F: bw loss, AST↑, ALT↑, urinary volume↓, liver necrosis **0.125**: mortality (3M), M: bw gain↓, food cons.↓, mono↑, AST↑, ALT↑, urinary volume↓, liver necrosis
CD2007/00966/ 00 (G07043)	Beagle dog 3/sex/group + 2/sex/group recovery	Oral gavage M: 0, 0.025, 0.038, 0.075 F: 0, 0.015, 0.020, 0.025	3 weeks + 2 weeks recovery	M: < 0.025 F: < 0.015	**≥ 0.015**: F: ret↓, cholesterol↑ **≥ 0.025**: mono↑, WBC↑, M: neut↑, food cons.↓, ret↓, F: GLDH↑, ALT **≥ 0.038**: mortality (1M), M: subdued behaviour watery feces, red/brown urine, ALT↑ **0.075**: mortality (3M), M: bw loss, food cons.↓, RBC parameters↓, APTT↑, ALP↑, GLDH↑, cholesterol↑, triglycerides↑, bone marrow myeloid hyperplasia, inflammation stomach and duodenum, lymphoid depletion thymus and GALT

Study ID	Species/Sex/ Number/Group	Dose/Route mg/kg/day	Duration	NOEL/ NOAEL mg/kg/ day	Major findings
CD2010/00179/ 00 (G09109)	Beagle dog 4/sex/group + 2/sex/group recovery	Oral gavage 0, 0.0075, 0.015, 0.03/0.023*	13 weeks + 4 weeks recovery	NOEL: M: 0.0075 F: NOAEL 0.015	**≥ 0.015**: ret↓, M: bw gain↓ **0.03**: mortality (1M), decreased activity, dehydration, RBC parameters↓, skin lesions, lymph node hemorrhage, M: food cons↓, GI toxicity (ulcer/erosion), F: bw gain↓
Non-pivotal studies					
CD2007/01374/ 00 (JTP74057-TX-0 02)	Rat 5M/group	Oral gavage 0, 0.3, 3, 30	3 days	< 0.3	**≥ 0.3:** ret↓, neut↑, lymph↓, myocard necrosis, aorta min, bone marrow hematop.cell necrosis, stomach min, kidney min **3:** mortality (1M) **≥ 3**: diarrhea, bw loss, food cons.↓, platelets↓, eos↓, AST↑, ALT↑, CP↑, LDH↑, bilirubin↑, BUN↑, creatinine↑, albumin↓, tp↓, P↑, Ca↓, triglycerides↑, Cl↓, myocard min, lymph node necrosis, thymus atrophy, lung min+ hemorrhage, stomach erosion, GI tract epithelial hyperplasia, liver min + necrosis + inflamm cells, kidney tubular necrosis, adrenal cortex necrosis **30**: ALP↑, cholesterol↑, spleen atrophy, GI tract erosion
CD2008/00267/ 00 (JTP74057-TX-0 03)	Rat 5M/group	Oral gavage 0, 0.1, 0.3, 1, 3	14 days	< 0.1	**≥ 0.1:** APTT↓, bone hypertrophy epiphyseal growth plate, skin lesions, stomach calcification **≥ 0.3**: AST↑, ALT↑, ALP↑, tp↓, P↑, kidney calcification, aorta calcification, bone marrow hematop.cell necrosis **≥ 1**: mortality (5M), decreased activity, diarrhea, bw loss, food cons.↓, ret↓, platelets↓, APTT↑, eos↓, LDH↑, bilirubin↑, BUN↑, creatinine↑, Ca↓, heart myocardial necrosis + calcification, liver necrosis + fatty change + calcification, lung calcification + hemorrhage, kidney tubular necrosis, stomach erosion, cecum ulcer + erosion, GI tract epith.hyperplasia, lymphoid necrosis lymph node + spleen + thymus, adrenal cortical necrosis, bone osteoblast hyperplasia + metaphysis degeneration **3**: mortality (5M), fibrinogen↓, tg↑

Study ID	Species/Sex/ Number/Group	Dose/Route mg/kg/day	Duration	NOEL/ NOAEL mg/kg/ day	Major findings
CD2008/00141/ 00 (JTP74057-TX-0 06)	Rat 5M/group + 5M/group recovery	Oral gavage 0, 0.1, 0.3	14 days + 14 days recovery	< 0.1	**≥ 0.1**: skin lesions, bone hypertrophy epiphyseal growth plate, min / calcification stomach, kidney, cornea **0.3**: neutrophils↑, mono↑, lymphocytes↓, AST↑, ALT↑, albumin↓, P↑, proteinuria, liver necrosis, bone marrow hypocellularity
CD2006/01117/ 00 (D06269)	Rat 4/sex/group + 3/sex/group TK	Oral gavage 0, 0.1, 0.3, 1	14 days	M: NOAEL 0.1 F: < 0.1	**≥ 0.1**: neut↑, F: bw loss, food cons.↓, lymph↑ **≥ 0.3**: M: WBC↓, lymph↓ **1**: stomach min, AST↑, M: bw loss, F: mono↑, skin ulceration and inflammation, liver vacuolation, femore-tibial joint growth plate retained cartilage
CD2006/01957/ 00 (D06431)	Rat 4/sex/group + 3/sex/group TK	Oral gavage 0, 1, 2, 3	14 days	< 1	**≥ 1**: mortality (4M, 4F), decreased activity, dehydration, food cons.↓, bw loss, neut↑, monocytes↑, ALT↑, AST↑, lymphocytes↓, RBC↓, ret↓, glucose↓, chol↓, tg↓, tp↓, skin lesions, liver necrosis and vacuolation, kidney tubular degeneration + min, heart myofiber necrosis + min, aorta min, bone subepiphyseal infarcts, stomach erosions + min, lung alveolar septae min, ovaries cystic follicles, intestines erosion + hyperplasia, mammary gland acinar epithelial necrosis + vacuolation, thymus atrophy **2**: mortality (4M, 4F), myocardial haemorrhage, F: adrenal cortex necrosis **3**: mortality (4M, 4F)
CD2006/01539/ 00 (D06330)	Beagle dog 1/sex/group	Oral gavage 0.125, 0.25, 0.5	10 days	< 0.125	**≥ 0.125**: bw loss, food cons.↓, ret↓, GI toxicity, bone marrow cellularity↓ **≥ 0.25**: mortality (1M, 1F), RBC parameters↓, platelets↓, tp↓, WBC↑, neut↑, mono↑, lymph↓, P↑, ALP↑, lymphoid necrosis, M: brown/red urine, bilirubin↑, AST↑, ALT↑, cholesterol↑, serum urea↑, F: ret↓ **0.5**: mortality (1M, 1F), M: ret↓
Combination study					

Study ID	Species/Sex/ Number/Group	Dose/Route mg/kg/day	Duration	NOEL/ NOAEL mg/kg/ day	Major findings
2011N112335_00 (G10260)	Beagle dog 3/sex/group	trametinib / dabrafenib: oral gavage / capsule (dose divided over 2 occasions/day) 0/0, 0.0075/5, 0.0225/20	4 weeks	< 0.0075/5	**≥ 0.0075/5:** bw gain↓, food cons.↓, stomach granulomatous inflammation, lymph node foreign material / histiocytosis, M: testis degeneration germinal epithelium, degenerate spermatids, thymus cellularity↓ **0.0225/20:** mortality (1m, coronary artery degeneration and inflammation), M: epididymis oligospermia, F: WBC, neut↑, mono↑, albumin↓, ALP↑, urinary volume↑

bw=body weight; M=male; F=female; P=serum inorganic phosphorus; TK=toxicokinetics; WBC=white blood cells; neut=neutrophils; min=mineralization; RBC=red blood cells; chol=cholesterol; tg=triglycerides; tp=total protein; GI=gastrointestinal; ret=reticulocytes; mono=monocytes; eos=eosinophils; lymph=lymphocytes;

bw=body weight; M=male; F=female; P=serum inorganic phosphorus; TK=toxicokinetics; WBC=white blood cells; neut=neutrophils; min=mineralization; RBC=red blood cells; chol=cholesterol; tg=triglycerides; tp=total protein; GI=gastrointestinal; ret=reticulocytes; mono=monocytes; eos=eosinophils; lymph=lymphocytes; HB=haemoglobin; Ht=haematocrit; CP=creatine phosphokinase; ALT=alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; LDH=lactate dehydrogenase; APTT=activated partial thromboplastin time

* Dosing of 0.03 mg/kg/day was stopped on day 11/12. Dosing resumed on day 21 at 0.023 mg/kg/day.

Genotoxicity

A standard package of genotoxicity studies was conducted with trametinib. In studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells and micronuclei in the bone marrow of rats, trametinib was not genotoxic.

Carcinogenicity

Carcinogenicity studies were not performed with trametinib. In accordance with ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals, carcinogenicity studies are not necessary for the approved indication.

Reproduction toxicity

The results from the Reproduction toxicity studies with trametinib are summarised in the table below:

Table 3: Reproductive toxicity studies with trametinib

Study type/ Study ID / GLP	Species; Number Female/ group	Route & dose mg/kg/day	Dosing period	Major findings	NOAEL (mg/kg &AUC)
Embryo-foetal development/ 2010N109544_01/ G10218 / GLP	Rat 21-22 F/group or 4F/group (high dose)	0, 0.062/0.016*, 0.094/0.031, 0.125/0.062, 0.375/0.125 Oral gavage	GD 6-17 C-section GD21	**≥0.062/0.016:** F0: bw gain↓ **≥0.094/0.031:** F1: foetal bw↓ **≥0.125/0.062:** F0: scabs **0.375/0.125**: F0: food cons↓, post-implant loss↑	F0: < 0.062/0.016 F1: 0.062/0.016 AUC 52.3 ng*h/ml
Embryo-foetal development / 2011N117363_01/ D11104 / non-GLP	Rabbit 4 F/group	0, 0.077/0.0385*, 0.154/0.077, 0.308/0.154, 0.616/0.308 Oral gavage	GD 7-19 C-section GD29	**≥0.077/0.385**: F0: bw gain↓ **≥0.154/0.077**: F1: foetal bw↓ **≥0.308/0.154**: F0: abortion **0.616/0.308**: F0: mortality (1), bw loss, 100% litter resorption	F0: < 0.077/0.385 F1: 0.077/0.385 AUC 22.4-54.7 ng*h/ml
Embryo-foetal development/ 2011N124059_00/ G11166/ GLP	Rabbit 22 F/group	0, 0.077/0.0385*, 0.154/0.077, 0.308/0.154 Oral Gavage	GD 7-19 C-section GD29	**≥0.077/0.0385:** F0: bw gain↓, F1: foetal bw↓, skeletal variations **0.308/0.154**: F0: food cons.↓, abortion, F1: skeletal anomalies	F0: < 0.077/0.0385 F1: < 0.077/0.0385 AUC 31.9 ng*h/ml
Juvenile toxicity/ 2012N146940_00/ D11083/ non-GLP	Rat 10 or 18/sex/group	0.04/0.02*, 0.13/0.06, 0.43/0.21, 1.3/0.64, 4.3/2.1	PND 7-21		0.04/0.02 AUC 600-710 ng*h/ml
		Or 0, 0.1, 0.02, 0.05	PND 7-35	**≥0.05**: dehydration, hyperpnoea, bw gain↓	
		Or 0, 0.05/0.08**, 0.05/0.17, 0/0.08, 0/0.17	PND 7-35	**≥0.13/0.06:** mortality, motor activity↓, bw loss	
		Oral gavage			

GD=gestation day; bw=body weight; PND=post-natal day; F=female; M=male

* First dose indicates a single loading dose on the first day of treatment. Second dose indicates maintenance dose which was given on the remaining days of treatment.

** The first dose was given on post-natal days 7-21. The second dose (a higher dose) was given on post-natal days 22-35 due to decreased exposure between post-natal days 13-21.

In accordance with ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals, no fertility nor pre- and post-natal development studies were conducted with trametinib.

Toxicokinetic data

The toxicokinetics show that trametinib exposure in animals is very low in comparison to human (0.08-1.32xhuman based on C_{max} and 0.09-1.24xhuman based on AUC). There was no clear effect of co-administration of trametinib or dabrafenib on the exposure to each agent in dogs.

Table 4: Toxicokinetics

Species/Study/ Duration	Dose (mg/kg/day)	Sex	C_{max} (ng/ml)		AUC (ng*h/ml)	
			End of study	Animal to human ratio[a]	End of study	Animal to human ratio[a]
Rat/G07042/3 weeks	0.016	M	1.78	0.08	35.0	0.09
		F	3.33	0.15	60.2	0.16
	0.031	M	3.5	0.16	64.2	0.17
		F	6.28	0.28	126	0.34
	0.062 (MTD)	M	7.78	0.35	129	0.35
		F	13.0	0.59	211	0.57
	0.125 (MTD)	M	13.3	0.60	218	0.59
		F	29.4	1.32	460	1.24
Rat/G09108/13 weeks	0.016	F	5.30	0.24	102	0.28
	0.031	M	5.34	0.24	95.4	0.26
		F	8.03	0.36	158	0.43
	0.062	M	15.4[b]	0.69	277[b]	0.75
		F	16.1[c]	0.73	287[c]	0.78
	0.125	M	NC	NC	NC	NC
Rat/R27719/48 hours	1	M/F	99.575-131-325	NC	ND	ND
	2	M/F	232.001-277.721	NC	ND	ND
Rabbit/G11166/2 weeks	0.0385	F	2.1[d]	0.09	31.9	0.09
	0.077		3.55	0.16	56.4	0.15
	0.154		8.93	0.40	127	0.34
Dog/G07043/3 weeks	0.015	F	7.19	0.32	120	0.32
	0.020[e]	F	11.6	0.52	211	0.57
	0.025 (MTD)[e]	F	12.3	0.55	205	0.55
		M	9.37	0.42	159	0.43
	0.038[e]	M	19.0[f]	0.86	282[f]	0.76
	0.075[e, g]	M	NC	NC	NC	NC

Dog/G09109/13 weeks	0.0075	M	2.32	0.10	45.6	0.12
		F	2.71	0.12	51.8	0.14
	0.015	M	5.15	0.23	95.5	0.26
		F	7.24	0.33	107	0.29
	0.023 (NOEAL)[h]	M	8.42	0.38	128	0.35
		F	9.78	0.44	150	0.41
Dog/G102260/4 weeks	Trametinib					
	0.0075	M	3.67	0.165	66.9	0.18
		F	3.47	0.156	66.5	0.18
	0.0225	M	11.5	0.52	223	0.60
		F	9.45	0.43	182	0.49
	Dabrafenib		ug/ml		ug*h/ml	
	5	M	2.38	1.16	23.1	0.39
		F	2.86	1.40	31.1	0.53
	20	M	6.18	3.00	82.1	1.39
		F	7.13	3.48	82.6	1.40
Human	Trametinib 2 mg	M/F	22.2	NA	370	NA
Human	Dabrafenib 150 mg BID	M/F	(ug/ml)	NA	ug*h/ml	NA
			2.05		58.9	

a = Ratios given with respect to mean human exposures on Day 15 of daily dosing at a dose of 2 mg.

b = Data obtained from 2 rats.

c = Data obtained following 4 weeks of dosing.

d = Data obtained from Day 5 of dosing.

e = Data obtained from 5 dogs.

f = Data obtained from 4 dogs.

g= For dogs given 0.075 mg/kg/day, the last day of dosing was Day 7.

h = Dogs received 0.030 mg/kg/day for first 11 to 12 days, an approximate 7 day drug holiday and then 0.023 mg/kg/day for the remainder of the study.

NA = Not applicable.

NC = Not calculated.

Local Tolerance

Local tolerance studies with trametinib were carried out. These studies included in vitro ocular and skin irritancy studies. (Table 21).

Table 5: Local tolerance

Type of test / study ID / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results Positive / negative / equivocal
SkinEthic, reconstructed human skin epidermal model/2010N111280_00/GLP	In vitro	25 mg for 10 or 60 minutes	Trametinib was considered to be a non-irritant
SkinEthic, reconstructed human corneal Epithelial model model/2010N1114680_00/GLP	In vitro	30 mg for 10 or 60 min	Trametinib was considered to be a non-irritant
Skin sensitization: Local lymph node assay/2012N131888_00/GLP	Mouse/5F	1% w/w, topical	Administration of trametinib resulted in a stimulation index (H3-thymidine incorporation into draining lymph nodes) of >3 in the absence of systemic toxicity or local irritation and therefore was considered to be a sensitizer.

Other toxicity studies

Antigenicity and Immunotoxicity studies

Other toxicity studies included antigenicity and immunotoxicity studies. A mouse lymph node assay carried out to assess antigenicity showed that trametinib was a skin sensitiser.

Regarding the immunotoxicity of trametinib, in the repeated dose toxicity studies done on rats with a daily oral dosing for up to 13 weeks, it was shown that the principal immune-related adverse effect was bone marrow degeneration/necrosis and lymphoid necrosis in lymph nodes, spleen and thymus. In addition, adverse skin and gastric changes were associated with inflammation, characterized by increased cellularity (lymphocytes and plasma cells) in lymph nodes and decreased circulating mean lymphocyte counts (up to 63%). In these rats there was an increase in circulating leukocyte counts (neutrophils and monocytes), bone marrow myeloid hyperplasia, and increased extramedullary haematopoiesis in the spleen. All adverse findings had reversed or partially reversed at the end of the recovery period.

The same gastrointestinal and hematopoietic perturbations were seen in studies on dogs under the same experimental conditions as for rats. Furthermore, in the dog 4-week combination study in which dogs were treated with trametinib and dabrafenib, decreased lymphoid cellularity of the thymus was observed at a lower dose than in the 3-week dog study in which only trametinib was given.

Metabolites

Active metabolites were metabolites M5 and M7; M5 with the same potency as trametinib and M7 with tenfold lower potency. Both metabolites did not account though for more than 10% of the drug-related material.

Studies on impurities

All impurities were specified below the qualification limit. Impurities that raised alerts for genotoxicity in in silico screening software (Derek version 13) were either controlled around or below the TTC of 1.5 µg/day or tested negative in an Ames test.

Phototoxicity

Trametinib absorbs light in the range 290 - 700 nm and it is distributed to the skin. Also, molar extinction coefficient values ≥ 1000 L mol^{-1} cm^{-1} were found at several wavelengths in the region of concern for photosafety at 314 and 337 nm. A quantitative whole body autoradiography (QWBA) study in pigmented rats showed a wide tissue distribution of drug-related material, including the skin. In oral repeat dose toxicity studies of up to 13 weeks in rats and dogs, no toxicity has been identified in the eye; however, there were findings in the skin (acanthosis, ulceration, exudation and inflammation) of rats and dogs.

2.3.4. Ecotoxicity / environmental risk assessment

Table 6: Summary of main study results

Substance (INN / Invented Name): Trametinib dimethyl sulfoxide			
CAS-number (if available): 1187431-43-1 or 871700-17-3 (trametinib)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential – log K_{ow}	OECD107	log K_{OW} = 4.04	not B
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	log K_{OW} = 4.04	not B
	BCF	no data, not evaluated	
Persistence	DT50 or ready biodegradability	no data, not evaluated	
Toxicity	NOEC or CMR	no data, not evaluated	
PBT-statement	trametinib is not PBT, nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined F_{pen}	0.0024 (refined based on prevalence)	µg/L	< 0.01 threshold
Other concerns (e.g. chemical	not investigated		

class)			

2.3.5. Discussion on non-clinical aspects

Trametinib is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and kinase activity. MEK proteins are components of the extracellular signal-related kinase (ERK) pathway. In melanoma and other cancers, this pathway is often activated by mutated forms of BRAF which activates MEK. Trametinib inhibits activation of MEK by BRAF and inhibits MEK kinase activity. Trametinib inhibits growth of BRAF V600 mutant melanoma cell lines and demonstrates anti-tumour effects in BRAF V600 mutant melanoma animal models.

Metabolites M5, M6 and M7were identified in in vitro studies and were all products of deacetylation. Deacetylation is likely mediated by hydrolytic esterases, although the applicant did not investigate the enzyme(s) responsible for trametinib metabolism. M5 is a pharmacologically active metabolite with the same potency as trametinib. As the protein binding data of M5 indicated that it contributes to well below the 50% threshold of pharmacological activity, further assessment of M5 as a substrate or inhibitor of drug transporters is not warranted (EMA Guidance on the Investigation of Drug Interactions).Because of the potential risk that patients who became progressive after treatment with trametinib would not respond anymore to BRAF inhibitors, the applicant was requested to discuss the development of resistance on monotherapy with trametinib. According to the applicant, whether a follow-up treatment can be successfully performed with a BRAF-inhibitor would depend on the type of mutation and no conclusion could be drawn from the limited non-clinical data. This issue is further discussed in section 2.6 of the AR.

In vitro and in vivo data suggest that trametinib is unlikely to affect the pharmacokinetics of other medicinal products. Based on in vitro studies, trametinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6 and CYP3A4. Trametinib was found to be an in vitro inhibitor of CYP2C8, CYP2C9 and CYP2C19, an inducer of CYP3A4 and an inhibitor of the transporters OATP1B1, OATP1B3, Pgp and BCRP. However, based on the low clinical trametinib systemic exposure (0.04 µM) relative to the in vitro inhibition or induction values (> 0.34 µM), trametinib is not considered to be an in vivo inhibitor of these enzymes/transporters although transient inhibition of BCRP substrates in the gut may occur (see SmPC section 5.2).

In vivo and in vitro data suggest that the PK of trametinib is unlikely to be affected by other medicinal products. As trametinib is metabolised predominantly via deacetylation mediated by hydrolytic enzymes, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions (SmPC section 5.2).

Trametinib is neither a substrate of CYP enzymes or of the efflux transporters P-gp nor BCRP. Trametinib is deacetylated via hydrolytic enzymes which are not generally associated with drug interaction risk. However, drug-drug interactions via these hydrolytic enzymes cannot be ruled out and could influence the exposure to trametinib (see SmPC section 5.2).

The applicant was requested to provide information whether trametinib is an inhibitor or substrate of liver transporters or renal transporters, in accordance with the EMA Guidance on the Investigation of Drug Interactions. While it is unlikely that trametinib at a low dose of 2 mg will affect the pharmacokinetics of other drugs, the risk cannot be fully excluded, therefore the applicant committed to investigate whether trametinib is an in vitro substrate of BSEP, MATE1 and MRP2 and whether trametinib exhibits transporter-mediated uptake by OATP1B1 and OATP1B3. In vitro inhibition studies for renal transporters OCT2, OAT1, OAT3 will also be submitted. The in vitro transporter studies for trametinib with final reports for all transporters are expected to be available by Q1 2015 (see RMP).

Dose separation of BCRP substrates and trametinib by 2 hours is likely sufficient to avoid any potential risk for a clinical drug interaction due to inhibition of BCRP by trametinib (see SmPC section 4.5).

Toxicology studies were carried out by the oral route of administration as this is the proposed therapeutic route in humans. The species and strains used in these investigations were selected on the basis of similarities in the pharmacokinetic and metabolic handling of trametinib between the selected species and humans. There was high level of sequence identity for MEK1 between the species used in non-clinical safety testing (~99%). For MEK2 the sequence homology is somewhat less (81-97%). However, none of the observed differences are located in the active site or in the predicted binding site of trametinib. In repeat-dose studies the effects seen after trametinib exposure are found mainly in the skin, gastrointestinal tract, haematological system, bone and liver. Most of the findings are reversible after drug-free recovery. In rats, hepatocellular necrosis and transaminase elevations were seen after 8 weeks at ≥ 0.062 mg/kg/day (approximately 0.8 times human clinical exposure based on AUC). In mice, lower heart rate, heart weight and left ventricular function were observed without cardiac histopathology after 3 weeks at ≥ 0.25 mg/kg/day trametinib (approximately 3 times human clinical exposure based on AUC) for up to 3 weeks (SmPC section 5.2). The preclinical findings indicate a low likelihood of myocardial necrosis caused directly by trametinib. The vascular and myocardial calcification seen in mice is believed to be a consequence of altered calcium phosphorus homeostasis. The potential cardiotoxicity is further discussed from a clinical point of view in sections 2.6 and 2.8 of this AR.

In rats, hypertrophy of the physis and increased bone turnover were observed, but the physeal hypertrophy is not expected to be clinically relevant for adult humans (SmPC section 5.2). The observations in adult rats were likely caused by the fact that in rats, the growth plates remain open until up to 60 to 80 weeks, whereas in humans, fusion and ossification of growth plates is completed by 20 years of age.

In rats, mineralisation of multiple organs was associated with increased serum phosphorus and was closely associated with necrosis in heart, liver, kidney and haemorrhage in the lung at exposures comparable to the human clinical exposure (SmPC section 5.2). Serum phosphorous is considered a suitable marker for soft tissue mineralization. The publication by Diaz et al (2012) states that increased serum phosphorous levels with soft tissue mineralization caused by MEK inhibition appears to be rat specific; it was not observed in mice, dogs or monkeys following the administration of the MEK inhibitor PD-901. If serum phosphorous is not increased in patients, the soft tissue mineralization that was observed in rats is not expected to be clinically relevant.

In rats and dogs given trametinib at or below clinical exposures, bone marrow necrosis, lymphoid atrophy in thymus and GALT and lymphoid necrosis in lymph nodes, spleen and thymus were observed, which have the potential to impair immune function (SmPC section 5.2).

Effects observed on the immune system were in some instances associated with inflammation resulting from effects on skin and gastrointestinal tract such as increased serum monocytes and neutrophils, increased cellularity in lymph nodes and decreased circulating lymphocytes.

Carcinogenicity studies with trametinib have not been conducted. Trametinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells and micronuclei in the bone marrow of rats (SmPC section 5.2).

In accordance with ICH S9, no fertility studies were conducted, however, trametinib may impair female fertility in humans, as in repeat-dose studies, increases in cystic follicles and decreases in corpora lutea were observed in female rats at exposures below the human clinical exposure based on AUC. However, in rat and dog toxicity studies up to 13 weeks in duration, there were no treatment effects observed in male reproductive tissues (SmPC section 5.2).

Based on the decrease in the numbers of copora lutea in non-pregnant rats, impaired female fertility may be possible. A warning regarding this possibility is present in sections 4.6 and 5.3 of the SmPC. Unlike rats and rabbits, in humans the corpora lutea supports pregnancy until the 50th day of gestation (approximately the 1st trimester) before a luteal to placental shift occurs (Itskovitz, 1988). Therefore, although the effect of trametinib on the functioning of corpus luteum of pregnancy is not entirely clear, the potential risk for human pregnancy is primarily limited to the first trimester.

In reproductive toxicity studies in rats and rabbits, trametinib induced maternal and developmental toxicity. In rats decreased foetal weights and increased post-implantation loss were seen at exposures below or slightly above the clinical exposures based on AUC. In pregnant rabbits, decreased foetal body weight, increased abortions, increased incidence of incomplete ossification and skeletal malformations were seen at sub-clinical exposures based on AUC (SmPC section 5.2). Based on all these observations, trametinib was considered teratogenic in rabbits in the high dose group, which actually corresponded to exposures below the clinical exposure.

Trametinib should not be administered to pregnant women or nursing mothers. If trametinib is used during pregnancy, or if the patient becomes pregnant while taking trametinib, the patient should be informed of the potential hazard to the foetus (SmPC section 4.6).

It is not known whether trametinib is excreted in human milk. Because many medicinal products are excreted in human milk, a risk to the breast-feeding infant cannot be excluded. A decision should be made whether to discontinue breast-feeding or discontinue trametinib, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman (SmPC section 4.6).

Proliferative skin lesions caused by dabrafenib alone when administered for at least 2 weeks were not observed in the combination study. Also in rats treated with another BRAF-inhibitor and another MEK1/MEK2-inhibitor, proliferative skin- and stomach lesions were diminished in the group treated with the combination. The limited data regarding trametinib-induced skin lesions that can be derived from the dog studies (effect much stronger in rats) suggest that skin toxicity caused by trametinib is not significantly increased by combination with dabrafenib.

No eye effects were observed non-clinically. There are however indications for eye toxicity caused by MEK inhibition in the literature. Eye toxicity has been observed from clinical experience and are further discussed in section 2.6 of the AR.

Phototoxicity has not been sufficiently investigated. The applicant will submit an in vitro study of phototoxicity potential post-approval (as reflected in the RMP).

The available data show that trametinib does not pose a potential risk to the environment.

2.3.6. Conclusion on non-clinical aspects

The non-clinical studies submitted for the marketing authorisation application for trametinib were considered adequate and acceptable for the assessment of non-clinical aspects for the product trametinib. The applicant will conduct additional in vitro studies post authorisation to further investigate phototoxicity. In addition further in vitro studies will be conducted to determine the enzymes responsible for the hydrolytic cleavage of trametinib, the potential for saturation of P-gp and BCRP and whether trametinib is a substrate of OATP1B1 and OATP1B3 and whether trametinib is an inhibitor of OCT2, OAT1, or OAT3 (see RMP).

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Protocol No.	**Study Objective(s)**	**Study Design**	**Key Inclusion Criteria of Subjects**	**No. of Subjects Gender Age (Range)**	**Treatment Details**	**Study Status**

MEK111054 (FTIH)	Determine the MTD of trametinib Characterize the PK of single- and repeat-dose trametinib Relationship between PK and PD/clinical endpoints	Phase I **Part 1**: FTIH, single- and repeat-dose escalation **Part 2**: Cohort expansion **Part 3**: PD Dose Range	**Part 1:** Subjects with solid tumours or lymphoma **Part 2:** Subjects with melanoma, pancreatic, CRC, NSCLC, or other tumour with BRAF mutation. CRC had to be KRAS or BRAF mutation-positive. **Part 3:** Subjects were to have a biopsiable tumour	206 subjects 112 M/94 F 58 yrs (19–92 yrs)	**Part 1:** Trametinib: **21/7 Regimen:** 0.125, 0.25, 0.5, 1, 2.0 mg once-daily dosing for 21 days, followed by 7 days without drug **Once-Daily Regimen**: 2.5, 3.0 or 4.0 mg continuous once-daily dosing **Once-Daily/Once-Daily Regimen** Once-daily doses ≤2.5 mg from Days 1 to 15, followed by once-daily dosing at 2.0 mg or 2.5 mg Once-Daily	Completed
MEK115064	Determination of the absolute bioavailability of trametinib	Phase I oral and IV microtracer study	Subjects with solid tumours.	4 subjects	Trametinib 2.0 mg, single dose, and 5 µg [^{14}C] trametinib, 15 minutes	Completed
MEK113708 (Mass balance)	Total recovery and relative excretion of radiocarbon in urine and faeces Compare total radiocarbon (DRM) in blood and plasma. Identify trametinib metabolites. Determine plasma trametinib PK parameters	Phase I	Subjects with solid tumours	2 subjects 2 M/0 F Age 54 and 66 yrs	Trametinib 2.0 mg containing approximately 79 µCi of radiocarbon. Solution(2 mg/5 ml) Single Dose	Completed

MEK113709	Food-effect study	Phase I	Subjects with solid tumours	24 subjects 10 M/ 14 F	Trametinib 2.0 mg with or without a high-fat meal	Completed
BRF113220	**Part A (DDI):** Determine the PK of single-dose dabrafenib alone and with repeat-dose trametinib Confirm steady state exposure to trametinib **Part B:** Characterize the steady state PK of dabrafenib and trametinib **Part D** (PK objectives): Determine SD and steady-state PK of dabrafenib alone and in combination with trametinib Determine SD and steady-state PK of trametinib	Phase I/II	Subjects with BRAF V600 mutation-positive melanoma and other solid tumours	**Part A:** 8 subjects 6 M/2 F 53 yrs (30-77 yrs) **Part B:** 66 subjects 35 M/31 F 53 yrs (25-78yrs) **Part D** (serial PK): 60 subjects 33 M/ 27 F 53 yrs (23-91 yrs)	**Part A:** Trametinib 2.0 mg Once-daily, Dabrafenib 75 mg Single dose **Part B:** Trametinib 1.0, 1.5, and 2.0 mg Once-daily, Dabrafenib 75 and 150 mg BID (150 and 300 mg daily) Continuous **Part D**: Dabrafenib 75 mg BID (150 mg daily) with trametinib 2 mg once daily Dabrafenib 150 mg BID (300 mg daily)	Ongoing (interim CSR)

MEK112111	Safety, tolerability, and recommended Phase II dose and regimen of trametinib and gemcitabine Characterize steady state PK of trametinib and gemcitabine	Phase IB study of trametinib in combination with gemcitabine	Subjects with solid tumours	31 subjects 13 M/18 F 58 yrs (25-76 yrs)	Trametinib 1.0, 2.0, and 2.5 mg Once-daily	Completed
MEK113583	Phase II efficacy and safety study PK Objective: Assess steady state exposure to trametinib and characterize the population PK including important determinants of variability.	Phase II	Subjects with BRAF V600 mutation positive melanoma	97 subjects 68 M/29 F 55 yrs (23-79 yrs)	Trametinib 2.0 mg Once-daily	Completed
MEK114267	Phase III, efficacy and safety study PK Objective: Characterize the population PK of trametinib and identify important determinants of variability Characterize the exposure-response relationship between trametinib and tumour size.	Phase III	Subjects with BRAF V600E/K mutation positive melanoma	Trametinib: 214 subjects 120 M/94 F 54 yrs (23–85)	Trametinib 2.0 mg Once-Daily	Completed

The applicant claimed the approval for the following indication:

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

Trametinib monotherapy is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Trametinib monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy (see section 5.1).

The final indication following CHMP review of this application is:

Trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Trametinib has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy (see section 5.1).

2.4.2. Pharmacokinetics

Absorption

After oral administration of 2 mg trametinib under fasted conditions, maximum plasma levels are obtained in approximately 1.5 hour. Geometric mean C_{max} ranged from 6.7 to 9.1 ng/ml after single-dose administration. Trametinib is classified as a highly permeable compound. The mean absolute oral bioavailability of trametinib 2 mg tablet was moderate to high, i.e. 72.3%, based on AUC_{0-t}. Based on the low solubility (consistent across all pH values) and moderate absolute bioavailability, it is considered a BCS class 4 drug.

Following single dose administration, trametinib AUC_{0-24} increased in a greater than dose-proportional manner with a mean slope (90% CI) of the power model of 1.30 (1.08-1.52), while increases in C_{max} were generally dose-proportional with a mean slope (90% CI) of the power model of 1.08 (0.90-1.25). Increases in Day 15 (steady-state) AUC_{0-24} and C_{max} were generally dose-proportional with once-daily doses of 0.125 to 4 mg, and this was confirmed in another study for the 1 to 2 mg dose range.

Steady state exposure is reached after approximately 15 days of OD administration of trametinib 2 mg. The accumulation factor is approximately 6.

The increase in exposure (C_{max} and AUC) was dose-proportional following repeat dosing. Following administration of 2 mg daily, steady state geometric mean C_{max}, AUC(0-t) and predose concentration were 22.2 ng/ml, 370 ng*hr/mL and 12.1 ng/ml, respectively with a low peak:trough ratio (1.8). Inter-subject variability at steady state was low (< 28 %).

Trametinib accumulates with repeat daily dosing with a mean accumulation ratio of 6.0 at 2 mg QD dose. Steady-state was achieved by Day 15.

The between-subject variability is larger for C_{max} (58%) compared to the variability observed with AUC (38%). The variability in C_{max} is lower after repeat daily dosing (28 to 36%) as trametinib accumulates about 6-fold due to its long half-life. No data on the intraindividual variation were obtained from pop-PK study 2011N120486_00.

Administration of a single, 2 mg oral tablet dose of trametinib with a high-fat, high-caloric meal affected both the rate and extent of absorption compared to fasting conditions with a 24 and 10% decrease in trametinib AUC_{0-t}, and AUC_{inf}, respectively, and a 70% decrease in C_{max}. Trametinib is recommended to be administered under fasting conditions, either 1 hour before or 2 hours after a meal, consistent with recommendations used in the Phase III study MEK114267.

Distribution

Plasma binding of trametinib is 97.4%. Trametinib accumulates to a limited extent in blood, with an in vitro blood:plasma ratio of approximately 3. Trametinib has a volume of distribution of approximately 1200 L determined following administration of a 5 µg IV microdose.

Following single dose administration of [14C]-trametinib as oral solution to two subjects, about 50% of circulating radioactivity in plasma wais present as the parent compound. Besides trametinib, deacetylated metabolite M5 and deacetylated/mono-oxygenated metabolite M7 were detected in plasma and accounted for <11% and <15% of plasma radioactivity, respectively. M6 (the N-glucuronide of M5) was also detected and its levels were variable between the 2 subjects (either <10% or <24% of plasma radioactivity). Based on limited results after repeat dosing of trametinib, >75% of drug-related material in plasma was parent.

Metabolism

Trametinib appears to be metabolised predominantly via deacetylation (non-CYP450 mediated) alone or with mono-oxygenation or in combination with glucuronidation 127. Although the specific enzyme responsible has not been identified, deacetylation is likely mediated by hydrolytic esterases, such as carboxylesterases or amidases.

Elimination

Trametinib terminal t1/2 is 127 hours (5.3 days) based on single dosing under fasted condition.

A mass-balance study (MEK113708) was performed where two male subjects with solid tumour malignancies received a single oral dose of [14C]-trametinib as an oral suspension (2 mg, 79 µCi) in fasted state. All plasma, blood, urine and faeces were collected at various times or intervals through 240 hours post-dose.

Faecal excretion appears the major route of elimination after [14C]-trametinib oral dose, with 81.3 and 94.3% of the excreted dose in 10 days (39.2 and 35% of the administered dose) in the two patients, respectively, excreted in the faeces, with parent, M5, and M7 identified. Biliary / gut excretion is estimated to account for more than 25% of the drug elimination and attempts will be made to identify the involved transporters (see discussion on non-clinical aspects). Urine is the minor excretory pathway (18.6 and 5.6% of the excreted dose, 9.0 and 2.1% of the administered dose excreted in 10 days) with urinary drug related material consisting of parent, M5, M7, and M9. M5 and M7 are the major radio-components in urine while parent trametinib (<0.1% of excreted dose) and M9 were minor components. Furthermore, after repeated dosing the metabolites M12, M13, M15 and M17 were also identified. In vitro all metabolites have been formed and M7, M12 and M17 were all shown to be formed via CYP3A4.

Geometric mean clearance (CL) was 3.21 L/hr after IV administration. Based on human liver blood flow of 81 L/hr and a blood:plasma ratio of approximately 3.4, trametinib CL is calculated to be approximately 1% of the liver blood flow.

Genetic polymorphism

Trametinib appears to be metabolized predominantly via deacetylation likely mediated by hydrolytic esterases. Based on current experience, no issues related to polymorphic esterases are expected.

Special populations

Impaired renal function

The effect of renal impairment on the PK of trametinib has not been investigated in a separate clinical study. In the two patients included in the mass balance Study MEK113708/11DMM005, less than 19% of the excreted dose (or <9% of the radioactive dose) was recovered in the urine as trametinib-related radioactivity and <0.1% of the excreted dose as trametinib parent. Based on the estimate of absolute bioavailability of 72.3%, the fraction that is excreted in the urine as trametinib is considered minimal. Renal impairment is unlikely to have a clinically relevant effect on trametinib PK given the low renal excretion of trametinib.

In the population PK analysis 2011N1204860, which included 223 and 35 subjects with mild (glomerular filtration rate [GFR] 60-<90 ml/min/1.73 m^2) and moderate (GFR 30-<60 ml/min/1.73 m^2) renal impairment, respectively, the effect of GFR on trametinib CL/F was small (<6% for both categories) and not clinically relevant. No data are available in subjects with severe renal impairment and thus the potential need for dose adjustment in patients with severe renal impairment cannot be determined.

Impaired hepatic function

The PK of trametinib has not been evaluated in a separate clinical study in subjects with hepatic impairment. A study in subjects with hepatic impairment is ongoing (see discussion on clinical pharmacology).

In the population PK analysis, 64 subjects (13%) were categorized as having mild hepatic impairment based on the classification (bilirubin ≤ULN and AST> ULN or bilirubin> 1X-1.5 x ULN, AST: any value). No data from subjects with moderate or severe hepatic impairment was available. Oral clearance was not significantly different between subjects with mild impairment and subjects with normal hepatic function (2% difference).

Gender

Based on the pop-PK study 2011N1204860, CL/F of trametinib was 26% higher in male than in female subjects. Pop-PK data from Study 2011N1204860 indicate that for a typical 79 kg subject, the pop-PK estimated mean CL/F (95% CI) were 4.91 (4.64-5.18) l/h for female and 6.19 (5.85-6.38) l/h for male subjects.

Race

The majority of subjects (97%) included in the supporting clinical trials were White. Therefore the effect of race was not tested in the pop-PK model.

Weight

Based on the pop-PK study 2011N1204860, CL/F of trametinib increased with body weight. For the range of weights in the pop-PK analysis (41.2 to 152 kg), Cl/F was within 15% of the typical value when compared within male or female subjects. Female or male subjects with minimum/maximum body weight (41.2 and 152 kg) had a predicted AUC and C_{max} within 15% and 30%, respectively, of the typical value observed with a median body weight of 79 kg.

Elderly

Based on the results of the population PK analysis, age as categorized in 3 groups <65 years (n = 351), 65 to <75 years (n = 114), and ≥75 years (n = 28) had no significant effect on trametinib exposure, with differences in trametinib CL/F between age groups of <13% for either category relative to non-elderly adults. The patient age ranged from 19 to 92 years.

Pharmacokinetic interaction studies

For in vitro studies, see non-clinical pharmacokinetics.

The Phase I/II dose-escalation Study BRF113220 investigated the safety, PK, PD and clinical activity of dabrafenib and trametinib in combination. The exposure of dabrafenib and its metabolites after a single 75-mg dose was not altered by co-administration of trametinib 2.0 mg once daily. Trametinib exposure did not change with co-administration of dabrafenib compared to historical monotherapy PK data (data not shown).

2.4.3. Pharmacodynamics

Exposure-efficacy relationship. Trametinib monotherapy

A trametinib monotherapy dose-response was observed for tumour markers pERK, Ki67 and p27, with lower pERK and Ki67 at higher trametinib dose, and higher p27 at higher dose. The observed inhibition of pERK, Ki67 and increases in p27 confirms inhibition of the MAPK/ERK pathway by trametinib, as a potential explanation of efficacy. At the 2 mg dose level, median trough concentration of trametinib on Day 15 was 14.4 ng/ml, which is above the pre-clinical target concentration of 10.4 ng/ml. The final 2.0 mg dose level for trametinib was selected based on the safety profile, PD and preliminary clinical activity in Study MEK111054. The 3 mg dose was demonstrated to be the MTD (see clinical efficacy, dose-response studies).

No clear trametinib exposure-PFS relationship was observed in the total patient population. Though in general, subjects with exposure above the median value had longer PFS than those below the median value with a HR <1, in all cases the HR 95% CI included the 1.0 no effect value. Correction for LDH, a known prognostic marker in subjects with melanoma, improved the results somewhat, to obtain a number of cases the HR 95% CI were <1.

The tumour size model that was developed indicates an effect of trametinib on tumour size, with a significant drug effect on the model parameter describing the development of progression after an initial decrease in tumour size. Subjects with higher exposure are predicted by the model to have a longer duration of response than those with lower exposures.

2.4.4. Discussion on clinical pharmacology

The analytical methods have been sufficiently validated and are considered sufficiently robust to allow reliable determination of trametinib, and its metabolites in plasma.

PK studies have been conducted in cancer patients. In all studies, patients with various types of solid tumours were included. In Study MEK111054, mostly melanoma patients were included, representing the targeted patient population. Relevant differences between the different kind of cancer patients are neither expected nor observed, and all PK data obtained in the various cancer patient populations are considered relevant to the melanoma population.

The composition of the commercial tablets was only changed to an insignificant extent as compared to the tablets used in the clinical trials. Therefore, it is agreed that no bioequivalence study is necessary to bridge between the clinical and commercial formulations.

The slight deviation from proportionality of the single dose trametinib AUC is not expected to negatively affect the use of trametinib in case dose reductions are applied in line with section 4.2 of the SmPC.

The different strengths of the trametinib tablets are not dose-proportional. However, considering the dose-proportional PK upon repeated administration of trametinib, comparative bioavailability studies between these tablet strengths are not considered necessary.

Based on currently available data, the clinical impact of the effect of food on trametinib exposure with repeat dosing is unclear. In Study MEK113709, decreases of 70%, 24%, and 10% were noted with C_{max}, AUC(0-last), and AUC(0-inf), respectively, when trametinib was administered with a high-fat, high-calorie meal relative to administration of trametinib under fasted conditions. Based on predicted mean concentration time profiles at steady-state (data not shown) the differences between fed/fasting predicted after repeat dosing were 46% for C_{max}, 24% for AUC(0-inf) and 31% for Cmin, with the point estimates of the differences between fed and fasting dosing outside the 80-125% acceptance criteria. Thus, it appears credible that there is a potential for a significant difference in C_{max} due to food intake. Given the lack of understanding regarding which pharmacokinetic parameter (C_{max} or AUC) drives the response, a specific recommendation to take trametinib in the fasting state has been included in the SmPC. Trametinib is recommended to be administered under fasting conditions, either 1 hour before or 2 hours after a meal, consistent with recommendations used in the Phase III study MEK114267. Trametinib should be taken orally with a full glass of water. Trametinib tablets should not be chewed or crushed (SmPC sections 4.2 and 5.2). Following single dose administration of [14C]-trametinib as oral solution, about 50% of circulating radioactivity in plasma is present as the parent compound. Based on limited results after repeat dosing of trametinib, >75% of drug-related material in plasma is parent. The reason for this difference (50% vs >75%) is not completely understood, but may be related to e.g. the low number of patients included, the use of a non-validated method in Study 09DMM056, the different dose, the dose-dependent blood:plasma ratio, and accumulation of trametinib.

Trametinib was the most abundant substance in plasma. Unbound plasma levels of other metabolites in plasma were lower than that of trametinib, and/or their activity was lower. Therefore the parent trametinib is considered responsible for activity of trametinib.

The popPK data regarding renal impairment suggest no effect of mild or moderate renal impairment. Based on the limited importance of renal excretion for trametinib clearance, the lack of a study in renally impaired patients is considered agreed. In light of the lack of data in severe renally impaired patients, caution is advised as reflected in section 4.2 of the SmPC.

The high absolute bioavailability and low CL suggest low hepatic extraction of trametinib in addition to low first-pass metabolism, hence trametinib is considered a low hepatic clearance drug.

Data for moderate and severe hepatically impaired patients are currently missing. The exposure to trametinib may be expected to be increased as hepatic disease affects metabolism, transport and biliary excretion which are the primary routes of elimination of trametinib. The population PK analysis indicated no significant effect of mild hepatic impairment on the PK of trametinib. However, hepatic function was only determined based on bilirubin and AST in this study, none of which might be a good marker for metabolic impairment. Nevertheless, it is currently acceptable not to include a specific warning in the SmPC for mild hepatic impairment, as MTD has not been reached with the 2mg QD dosing. Study MEC116354, a Phase I and pharmacokinetic study evaluating trametinib in patients with hepatic dysfunction is being conducted under the US National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP). The Applicant has committed to submit the final study report after completion of the study in Q4 2017. Until such further data regarding moderate and severe hepatic impairment are available, trametinib should be used with caution in such patients (SmPC section 4.2).

Based on a population pharmacokinetic analysis, gender and body weight were found to influence trametinib oral clearance. Based on additional analyses (data not shown), the effect of sex on CL was partially attributed to weight differences, and heavier patients were predicted to achieve a lower exposure of unclear magnitude. To further evaluate the effect of body weight, the applicant presented efficacy data (ORR and PFS) from the phase III study stratified according to quartiles of body weight. No treatment by covariate interaction with body weight was observed for PFS, whilst ORR was lower (15%) in heavier patients relative to other groups (21 to 25%). However, the differences were not statistically significant and based on the totality of data, patients with high body weight responded similarly to treatment with trametinib as patients with lower body weight. In conclusion, although lower weight female subjects are predicted to have higher exposure than heavier male subjects, these differences are unlikely to be clinically relevant and no dosage adjustment is warranted (SmPC section 5.2).Although the potential for drug-drug interactions for trametinib seems low, relevant in vivo inhibition of intestinal BCRP in the intestine cannot be excluded based on in vitro data (see discussion on Non-clinical aspects).

No initial dose adjustment is required in patients > 65 years of age.

Based on non-clinical data, trametinib should be considered a potential human teratogen, and according to the Guideline on the Investigation of Drug Interactions, for such substances a study for the in vivo effects on oral contraceptives has to be performed regardless of in vitro induction results. Until data on this potential interaction are available, the SmPC indicates that highly effective contraception should be used by female patients during treatment with trametinib and for 4 months after treatmen . The applicant is recommended to conduct a drug interaction study (Study MEK113707) with an oral contraceptive to assess the effect of repeat-dose trametinib on the repeat-dose pharmacokinetics of ethinyl estradiol and norethindrone. Until data on this potential interaction are available, effective contraception should be used by patients as well as their partners. To prevent pregnancy, female patients using hormonal contraception are advised to use an additional or alternative method during treatment and for 4 months following discontinuation of trametinib (SmPC section 4.6).

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 (data not shown). There was no evidence that the increase in pyrexia was related to trametinib exposure. The lack of data in children <18 years is indicated in the SmPC section 4.2.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of trametinib has been adequately investigated. Additional data will be provided by the Applicant in relation to special patient populations and drug metabolism.

2.5. Clinical efficacy

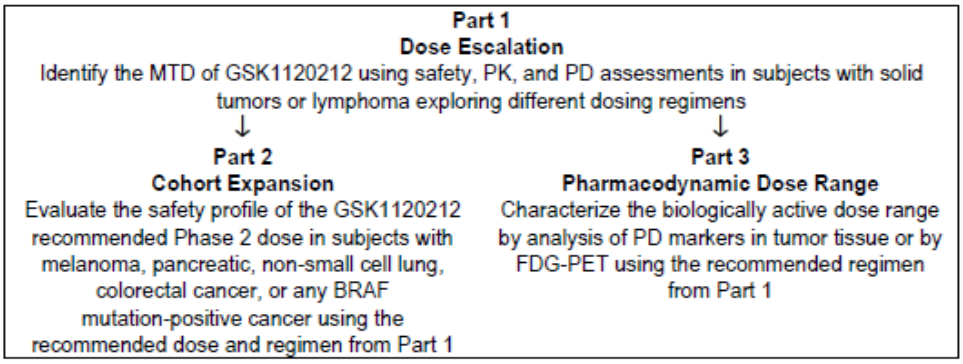
2.5.1. Dose response study(ies)

The dosage for trametinib that is recommended for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation is 2.0 mg orally QD (once daily). This dose was selected based on safety and tolerability and also on exposure-response relationship with tumour and clinical activity. From preclinical studies it was already known that the target trametinib concentration of >10.4 ng/mL could be achieved with the oral intake of 2 mg trametinib daily.

Monotherapy:

The phase I study MEK111054 was an open-label, multiple-dose, multicenter (12, all US), dose-escalation study to investigate the safety, pharmacokinetics, and pharmacodynamics of the trametinib in subjects with solid tumours or lymphoma.

Study period: Initiation Date: 31 July 2008 (First Subject First Visit), Completion Date: 07 June 2011 (Data cut-off date for study report)



Regimens

Parts 1 and 2:

21/7 Regimen: Once daily (QD) dosing for 21 days, followed by 7 days without drug.

LD Regimen: One or two loading doses (LD) followed by continuous QD dosing (abbreviated LD/QD or LD/LD/QD regimen)

QD Regimen: Continuous QD dosing (abbreviated QD regimen)

Part 3:

QD/QD Regimen: Continuous QD dosing at ≤2.5 mg QD from Days 1 to 15, followed by continuous QD dosing at either 2.0 mg or 2.5 mg (abbreviated QD/QD).

Results

In this study the maximum tolerated dose was defined as 3 mg QD. Dose limiting toxicities (DLT) were rash (grade 3, 2 pts), diarrhea (grade 3, 1 patient) and chorioretinopathy (grade 2, 2 patients). The incidence of AEs ≥ grade 3 in the 2.0 mg QD dose group was considered acceptable (14%) when compared with the higher 2.5 and 3 mg QD dose groups (23 and 31% respectively). With the 2 mg QD no AE grade ≥ 4 was encountered.

Based on the safety, efficacy, PD and PK data from this study trametinib 2.0 mg once-daily was chosen as the dose to be administered in study MEK113583 and pivotal study MEK114267.

Combination therapy:

The Phase Ib/II study BRF113220 was an open-label, dose-escalation, multicentre (2 Australia, 12 US) study to investigate the Safety, pharmacokinetics, pharmacodynamics and clinical activity of dabrafenib in combination with trametinib in subjects with BRAF Mutant Metastatic Melanoma (Parts A,B,D).

Part B of the study was the dose escalation part. For further details on the study methods, (see section 2.5.2).

	Objectives	Endpoints
Primary	To determine the safety, tolerability and range of tolerated doses of dabrafenib and trametinib dosed orally in combination in subjects with BRAF V600 mutation positive metastatic melanoma	Adverse events and changes in laboratory values and vital signs
Secondary	To characterize the steady-state PK of dabrafenib (and its metabolite(s) including hydroxydabrafenib), and trametinib.	Dabrafenib (and its metabolite(s) including hydroxydabrafenib), and trametinib PK parameters following repeat-dose (Day 15) administration of dabrafenib and trametinib, including area under the concentration-time curve over the dosing interval (AUC(0-τ)), trough concentration (Cτ), Cmax, and time of Cmax (tmax)
	To evaluate the clinical activity of dabrafenib and trametinib in subjects with BRAF mutant metastatic melanoma	Tumor response as defined by RECIST 1.1; Overall survival.
	To evaluate the pharmacodynamic response in BRAF mutant colorectal cancer pharmacodynamic cohort after treatment with dabrafenib and trametinib	Change in p-ERK and other biomarkers in tumor biopsies
	To explore relationships between dabrafenib, trametinib PK, MAPK signalling inhibition and clinical endpoints	

Subjects (n=135) were enrolled in escalating dose cohorts of dabrafenib and trametinib in a traditional "3(4) +3" design to identify the range of tolerated doses.

A dose-to-event relationship with regard to safety and efficacy for the different dabrafenib and trametinib combination regimen was not established. Therefore, in addition to the full monotherapy doses (150 mg BID of dabrafenib and 2 mg daily of trametinib), a second treatment group of dabrafenib 150 mg BID and trametinib 1 mg daily was selected for Part C in order to elucidate the contribution of trametinib to the combination regimen.

In part C of the Study BRF113220 the efficacy and safety of dabrafenib 150 BID in combination with 2 mg or 1 mg trametinib (QD) was compared with dabrafenib 150 BID monotherapy. The five most encountered AE with the combination treatment are pyrexia, chills, fatigue, nausea, and vomiting. In Study BRF113220 only trametinib doses up to 2 mg have been explored.

2.5.2. Main studies

2.5.2.1. Monotherapy: Study MEK114267

Methods

This was a phase III multicenter, randomized, open-label study comparing efficacy and safety of trametinib vs dacarbazine or paclitaxel, in patients with histologically confirmed cutaneous unresectable or metastatic melanoma (Stage IIIc or stage IV) with a BRAF V600E or V600K mutation.

Study Participants

Subjects were eligible to enter the study if they met all of the inclusion criteria and none of the exclusion criteria. Key inclusion criteria included:

- Histologically confirmed, Stage III unresectable (Stage IIIC) or metastatic (Stage IV) cutaneous melanoma, which is also determined to be BRAF V600E/K mutation-positive by the central reference laboratory.
- Subjects may have received no prior treatment or up to 1 prior regimen of chemotherapy for advanced or metastatic melanoma.
- Measurable disease according to RECIST v1.1.
- Adequate screening organ function as defined in Protocol Amendment 3, Section 4.1.2.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1.

Key exclusion criteria included the following:

- Any prior use of BRAF/MEK inhibitors, or ipilimumab in the advanced or metastatic setting.
- 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.
- History of other malignancy. Subjects who had been disease-free for 3 years or subjects 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 subject's safety, obtaining informed consent or compliance to the study procedures.
- Brain metastases with the following exceptions that are ALL confirmed by the sponsor Medical Monitor:
    - 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), or if no longer present, must be confirmed as no evidence of disease, for ≥90 days prior to randomization (must be documented with two consecutive MRI or CT scans at least 60 days apart using contrast), and
    - Asymptomatic with no corticosteroids requirement for ≥ 30 days prior to randomization, and
- No enzyme-inducing anticonvulsants for ≥ 30 days prior to randomization.
- History or evidence of cardiovascular risk.
- History or current evidence / risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR).

Treatments

Study treatments were trametinib (2 mg once daily under fasting conditions, i.e., at least 1 hour before a meal or at least 2 hours after a meal), or chemotherapy consisting of either dacarbazine (1000 mg/m2 every 3 weeks), or paclitaxel (175 mg/m2 every 3 weeks) at investigator discretion, provided the patient had not received that type of chemotherapy prior to randomization. Patients receiving chemotherapy were allowed to crossover to trametinib after confirmation of progression by independent assessment.

Objectives

The primary objective was to test the superiority of trametinib over chemotherapy with respect to progression-free survival (PFS) for melanoma patients with BRAF V600 mutation. The secondary objectives included the evaluation of:

- PFS in the subgroup of patients chemo naive and the subgroup who had received 1 prior chemotherapy in the advanced or metastatic setting;
- overall response rate (ORR) and duration of response (DoR) in patients with BRAF V600E mutation-positive melanoma; ORR and DoR in patients with BRAF V600K mutation-positive melanoma;
- efficacy (PFS, ORR, and DoR) in the overall study population and in patients following crossover from chemotherapy to trametinib;
- the safety and PK of trametinib in patients with metastatic melanoma.

Outcomes/endpoints

The primary endpoints of MEK114267 study originally were OS & PFS (co-primary endpoints). Before the data cut-off date, the primary endpoint was amended to PFS (investigator assessment).

The primary efficacy population was the subset of the ITT population with BRAF V600E subjects without a prior history of brain metastases

Secondary endpoints included PFS in ITT (also including patients with BRAF V600K mutation and/or history of brain metastasis) and subpopulations, OS in primary and ITT, ORR in primary and ITT and Duration of response, safety, PK.

Disease progression and response evaluations were determined according to the definitions established in the RECIST v 1.1, using radiological and clinical disease assessment for palpable lesions at baseline and at week 6, 12, 21, 30 and every 12 week thereafter.

Exploratory endpoints included evaluation of health related of quality of life (HRQoL), PK, PD, correlation of BRAF mutation in cfDNA with that in the tumour tissue, biomarkers (mutations in BRAF, MEK1/2,PTEN and other genes, and expression of genes and proteins), and pharmacogenetics. HRQoL was assessed with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) version 3 and the EuroQoL-5D (EQ-5D) at Screening; Weeks 6, 12, 21 and 30; and every 12 weeks (± 7days) until determination of progressive disease (PD), and 6 weeks following disease progression.

Sample size

A total of 322 patients were assessed for the ITT population, including 40 patients with BRAF V600K mutations, 1 patient with a BRAF V600 E/K mutation, and 11 patients with a prior history of brain metastases.

Randomisation

Before centralised randomization eligible patients were stratified for lactate dehydrogenase (LDH) (above upper limit of normal [ULN] vs. equal to or below ULN) and prior chemotherapy for advanced or metastatic disease (yes vs. no).

Subjects in each stratum were centrally randomized (randomized phase) through the Registration and Medication Ordering System (RAMOS) (Interactive Voice Response System [IVRS]).

Blinding (masking)

Not applicable

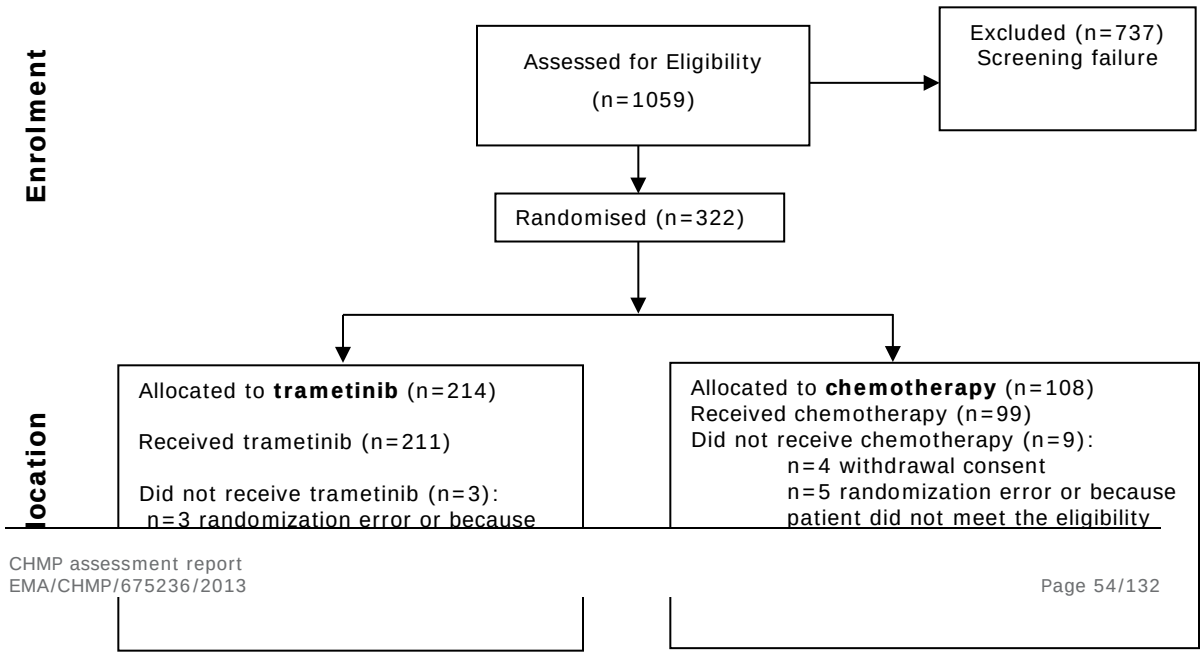
Statistical methods

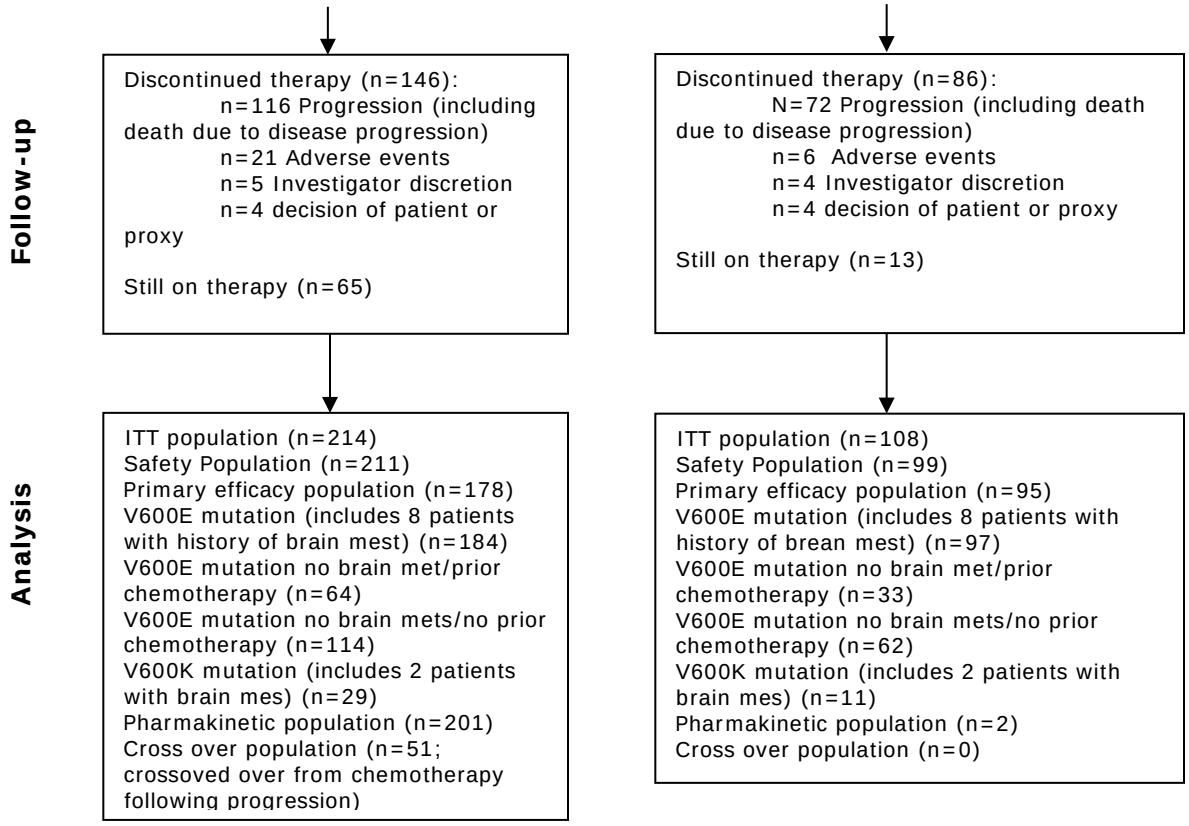
PFS was censored if there was more than one subsequently missed assessment visit, and if new therapy was started without scan-evidence of progression. Robustness of PFS for investigator bias was assessed by performing a blind independent review.

The impact of baseline covariates on PFS was investigated using a stepwise Cox regression (BRAF mutation (V600K vs. V600E), prior History of Brain Metastases (Yes vs. No), Prior treatment with chemotherapy for advanced or metastatic disease: (Yes vs. No), Prior immunotherapy (Yes vs. No), Baseline ECOG performance status: (0 vs. 1), Baseline LDH: (above ULN vs. equal to or below ULN), Stage at Screening (III, IVM1a, IVM1b vs. IVM1c), Visceral Disease at Baseline (yes/no), Number of disease sites at baseline (<3 vs. ≥3), Sex (Male vs. Female), Age (continuous)).

Results

Participant flow





**Mets= metastases; ITT=intent-to-treat*

Recruitment

Patients were enrolled by 86 sites in 19 countries from December 2010 to July 2011.

Conduct of the study

The original study protocol dated 24-august-2010, was amended 5 times. Main amendments consisted of:

1-Date 18 October 2010. The amendment changed the primary endpoint to PFS and added crossover to trametinib after progression on the chemotherapy arm bases on feedback from the European Medicines Agency (EMA), changed the ophthalmological guidelines, modified inclusion/exclusion criteria to allow prior treatment with ipilimumab in the adjuvant setting and patients with brain metastases meeting specific criteria.

2-Date 02 May 2011. The amendment changed eligibility criteria requiring documented disease progression prior to randomization, changed eligibility criteria for patients with brain metastases to indicate that prior whole brain radiotherapy was not allowed and confirmation of stable and/or no evidence of disease was required prior to randomization, allowed crossover after discontinuation of chemotherapy only after documentation of disease progression,

3-Date 03 October 2011. The amendment restricted the Primary Efficacy population to patients with a BRAF V600E mutational status without history of prior brain metastases.

4- Date 27 January 2012. The amendment included information, management and guidelines for monitoring and treatment of hypertension.

5- Date 5 February 2012. The amendment allowed immediate crossover, after advice of the Independent Data Monitory Committee of any patient enrolled in the chemotherapy arm.

Amendments 4 and 5 were effective after the data cut-off date.

Baseline data

Table 7: Principal demographic and Baseline Prognostic Factors (ITT Population study MEK114267)

	Trametinib (N=214)	Chemotherapy (N=108)	Total (N=322)
Age (years)			
Median (Min. – Max.)	54.5 (23-85)	54.0 (21-77)	54.0 (21 -85)
Age Category, n (%)			
<65 years	165 (77)	86 (80)	251 (78)
≥65 years	49 (23)	22 (20)	71 (22)
>75 years	9 (4)	3 (3)	12 (4)
Sex, n (%)			
Male	120 (56)	53 (49)	173 (54)
Female	94 (44)	55 (51)	149 (46)
Baseline lactate dehydrogenase, n (%)			
≤ULN	134 (63)	66 (61)	200 (62)
>ULN	77 (36)	42 (39)	119 (37)
Unknown	3 (1)	0	3 (<1)
Prior chemotherapy for advanced or metastatic disease, n (%)			
No	143 (67)	70 (65)	213 (66)
Yes	71 (33)	38 (35)	109 (34)
ECOG PS at Baseline, n (%)			
ECOG 0	136 (64)	69 (64)	205 (64)
ECOG 1	78 (36)	39 (36)	117 (36)
Stage at screening, n (%)			
IIIC, IV M1c, or IV M1b	69 (32)	45 (42)	114 (35)
IV M1c	144 (67)	63 (58)	207 (64)
Unknown	1 (<1)	0	1 (<1)
Visceral disease at Baseline, n (%)			
No	36 (17)	23 (21)	59 (18)
Yes	178 (83)	85 (79)	263 (82)
Number of disease sites at Baseline, n (%)			
≥3 sites	123 (57)	56 (52)	179 (56)
<3 sites	91 (43)	52 (48)	143 (44)
BRAF mutation status, n (%)			
V600E	184 (86)	97 (90)	281 (87)
V600K	29 (14)	11 (10)	40 (12)
V600E/V600K	1 (<1)	0	1 (<1)
History of brain metastases, n (%)			
No	205 (96)	106 (98)	311 (97)
Yes	9 (4)	2 (2)	11 (3)

The majority of patients in this study were white (>99%), with a median time since metastatic diagnosis of 7.29 months (range 0.16-204.22).

The most common (⩾20% in either treatment arm) locations of disease were lymph nodes, lung, liver, and subcutaneous tissue.

Table 8: Prior Anticancer Therapy (ITT Population MEK114267)

	Trametinib (N=214)	Chemotherapy (N=108)	Total (N=322)
Any therapy, n (%)	**200 (93)**	**101 (94)**	**301 (93)**
Surgery	193 (90)	98 (91)	291 (90)
Chemotherapy (cytotoxics, non-cytotoxics)	74 (35)	39 (36)	113 (35)
Immunotherapy	68 (32)	30 (28)	98 (30)
Radiotherapy	53 (25)	21 (19)	74 (23)
Biologic therapy (monoclonal antibodies, vaccines)	16 (7)	13 (12)	29 (9)
Hormonal therapy	1 (<1)	0	1 (<1)
Small molecule targeted therapy	0	1 (<1)	1 (<1)

Among trametinib treated patients, 35% received prior chemotherapy which was given in the adjuvant setting in 4% of patients and in the advanced or metastatic setting in 33% of patients. In the trametinib arm 32% received prior immunotherapy, preferentially as adjuvant therapy in 25% of patients and primarily with interferon. In the trametinib arm, 25% of patients received prior radiotherapy and 3 patients received prior ipilimumab primarily as adjuvant therapy (2 of the 3 patients). Dacarbazine was the most common prior anticancer therapy received for both treatment arms.

Numbers analysed

Study Populations

	Trametinib	Chemotherapy	Total
ITT population	214	108	322
Safety population	211	99	310
Primary efficacy population	178	95	273
V600E mutation (includes 8 subjects with history of brain mets)	184	97	281
V600E mutation no brain mets/prior chemotherapy	64	33	97
V600E mutation no brain mets/no prior chemotherapy	114	62	176
V600K mutation (includes 2 subjects with brain mets)	29	11	40
Pharmacokinetic population	201	2 [a]	203
Crossover population	51	0	51

Data Source: Table 6.1
Abbreviations: mets = metastases; ITT = intent-to-treat
Note: One subject had a V600E/K mutation and a history of brain metastases and was included in the ITT population, but excluded from the Primary Efficacy population (Table 9).
a. Protocol deviation: PK samples were obtained for 2 subjects on the chemotherapy arm.

Outcomes and estimation

Progression free survival (PFS)

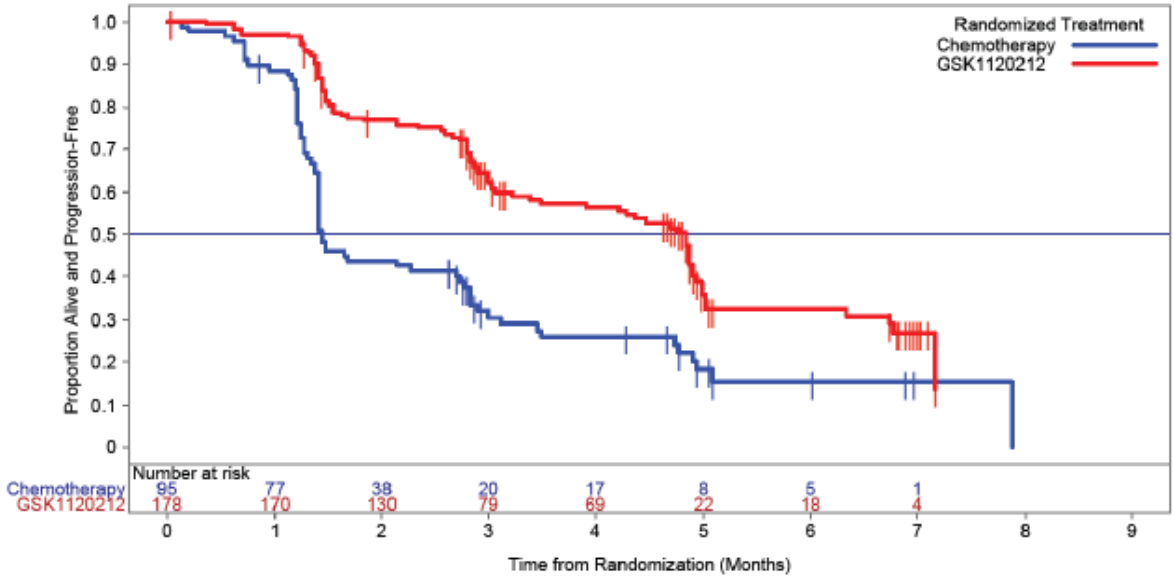
In the Primary Efficacy population, a statistically significant improvement in investigator-assessed PFS was observed in the trametinib group compared with the chemotherapy group

(Table 9 and Figure 2).

Table 9: Investigator-assessed-Kaplan-Meier estimates of PFS (primary efficacy population)

	Trametinib (N=178)	Chemotherapy (N=95)
Subject Classification, n (%)		
Progressed or died (event)	96 (54)	68 (72)
Censored, follow-up ended	8 (4)	8 (8)
Censored, follow-up ongoing	74 (42)	19 (20)
Adjusted hazard ratio [a]	0.44	
Estimate (95% CI)	(0.31,0.64)	
Stratified log-rank p-value [a]	<0.0001	
Kaplan Meier Estimate for PFS, (months) [b]		
1st quartile (95% CI)	2.6 (1.5,2.8)	1.2 (1.2,1.4)
Median (95% CI)	4.8 (3.5,4.9)	1.4 (1.4,2.7)
3rd quartile (95% CI)	7.2 (5.0,--)	4.7 (2.8,5.1)

Data Source: Table 7.3
Abbreviations: CI = confidence interval; PFS = progression-free survival
a. Hazard ratios are estimated using a Pike estimator. A hazard ratio <1 indicates a lower risk with trametinib compared with chemotherapy. Hazard Ratio and p-value from stratified log-rank test are adjusted for prior chemotherapy for advanced or metastatic disease and baseline LDH.
b. Quartiles estimated using the Brookmeyer-Crowley method.



Data Source: Figure 17.1
Abbreviations: PFS = progression-free survival
Notes: Vertical bars denote censored subjects.

Figure 2: Investigator-assessed Kaplan-Meier PFS curves (primary efficacy population)

Table 10: Investigator assessed efficacy results (ITT population)

Endpoint	Trametinib	Chemotherapy[a]
Progression-Free Survival	**(N = 214)**	**(N = 108)**
Median PFS (months) (95 % CI)	4.8 (4.3, 4.9)	1.5 (1.4, 2.7)
Hazard Ratio (95 % CI) *P* value	0.45 (0.33, 0.63) <0.0001	
Overall Response Rate (%)	22	8

ITT = Intent to Treat; PFS = Progression-free survival; CI = confidence interval.

[a] Chemotherapy included patients on dacarbazine (DTIC) 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 every 3 weeks.

[b] Median overall survival not reached at the time of analysis

In the primary efficacy population, IRC-assessed median PFS was 4.9 months with trametinib and 1.6 months with chemotherapy HR=0.41 (95% CI 0.29, 0.60, p<0.0001).

PFS in subgroups

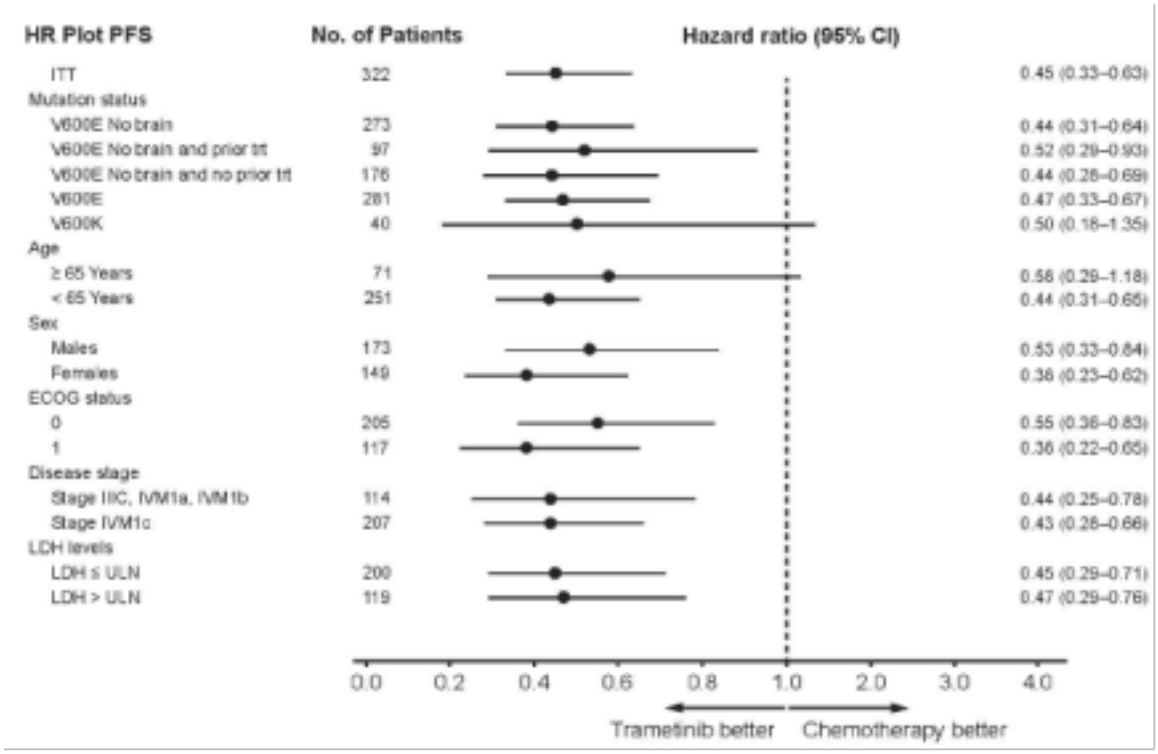


Figure 3: Forrest Plots for PFS in Subgroups (study MEK114267)

Secondary efficacy endpoint:

Overall Survival

OS was analysed at the time of the primary endpoint analysis of PFS. An updated analysis as of 20 May 2013 for MEK114267 has also been provided. At the time of this data cutoff, 65% of subjects on the chemotherapy arm crossed over to trametinib upon progression.

Table 11: Survival data from the primary and updated analyses (ITT population)

Cut-off dates	Treatment	Number of deaths (%)	Median months OS (95% CI)	Hazard ratio (95 % CI)	Percent survival at 12 months (95 % CI)
October 26, 2011	Chemotherapy (n=108)	29 (27)	NR	0.54 (0.32, 0.92)	NR
	Trametinib (n=214)	35 (16)	NR		NR
May 20, 2013	Chemotherapy (n=108)	67 (62)	11.3 (7.2, 14.8)	0.78 (0.57, 1.06)	50 (39,59)
	Trametinib (n=214)	137 (64)	15.6 (14.0, 17.4)		61(54, 67)

NR=not reached

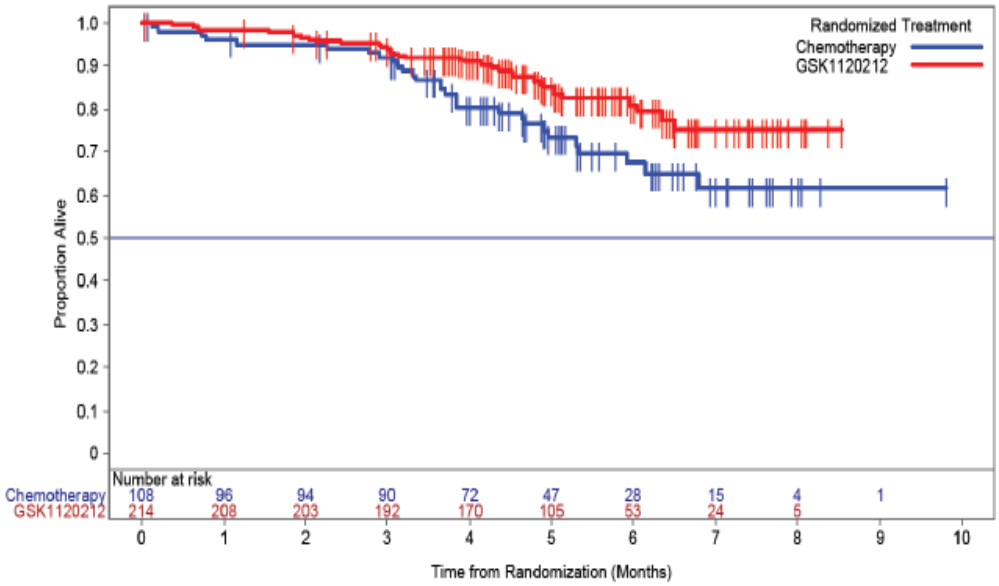


Figure 4: Kaplan-Meier curves of overall survival (ITT population; interim analysis)

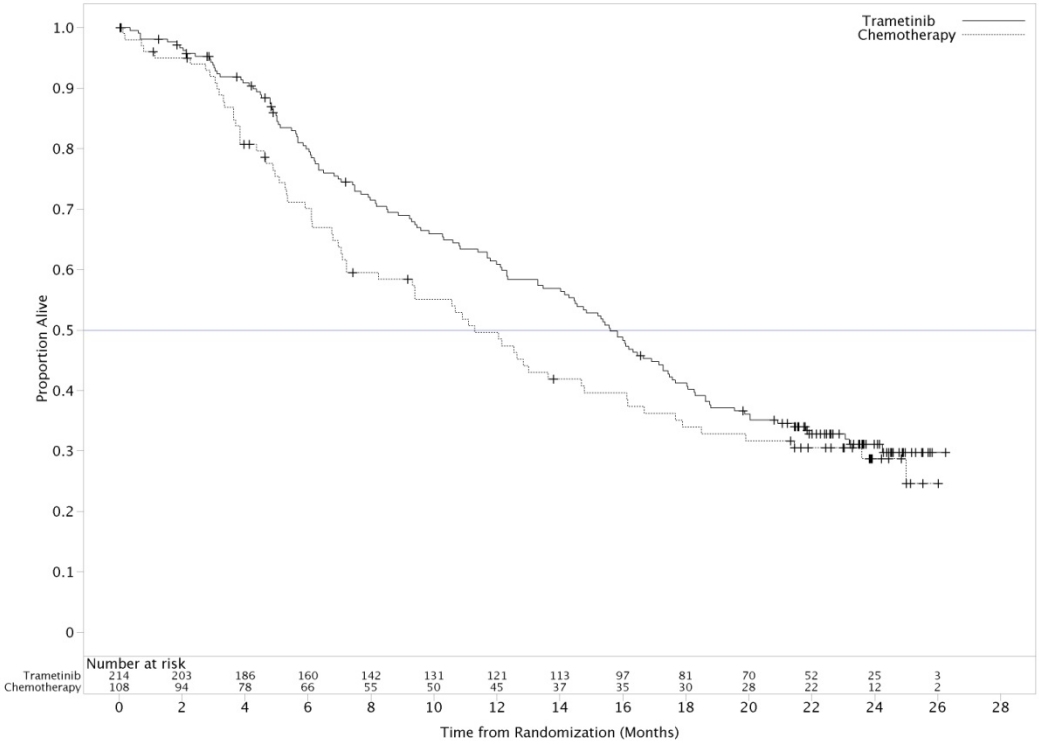


Figure 5: Kaplan-Meier curves of overall survival (ITT population updated analysis - 20 May 2013)

Overall Response Rate (ORR)

Table 12: Investigator-assessed best confirmed response (primary efficacy population)

	Trametinib (N=178)	Chemotherapy (N=95)
Best response (RECIST 1.1), n (%)		
Complete response	4 (2)	0
Partial response	39 (22)	7 (7)
Stable disease	92 (52)	31 (33)
Progressive disease	35 (20)	45 (47)
Not evaluable [a]	8 (4)	12 (13)
Response rate, n (%)		
CR+PR	43 (24)	7 (7)
95% CI	(18.1,31.1)	(3.0,14.6)
Difference in ORR, (%)		
Difference	17	
95% CI [b]	(5.4, 29.1)	
P-value [b]	0.0030	

Data Source: Table 7.98

Abbreviations: CI = confidence interval; CR = complete response; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors

a. Best response of Not Evaluable included subjects who withdrew consent, were withdrawn by the investigator, died, or started new anticancer therapy prior to first efficacy assessment (Listing 18.23, Listing 26.4, Listing 26.5, and Listing 26.23).

b. Fisher's exact test.

Table 13: Independent review-assessed best confirmed response (primary efficacy population)

	Trametinib (N=178)	Chemotherapy (N=95)
Best response (RECIST 1.1), n (%)		
Partial response	33 (19)	3 (3)
Stable disease	90 (51)	32 (34)
Non-CR/non-PD [a]	12 (7)	6 (6)
Progressive disease	30 (17)	42 (44)
Not evaluable [b]	11 (6)	12 (13)
Not applicable [c]	2 (1)	0
Response rate, n (%)		
CR+PR	33 (19)	3 (3)
95% CI	(13.1%,25.0)	(0.7%,9.0)
Difference in ORR, (%)		
Difference	15	
95% CI	(5.0, 27.2)	
P-value [d]	0.0027	

Data Source: Table 7.100

Abbreviations: CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors

a. Subjects identified as having only non-target lesions at Baseline.
b. Best response of "Not Evaluable" included subjects who withdrew consent, were withdrawn by the investigator, died, or started new anticancer therapy prior to first efficacy assessment (Listing 18.23, Listing 26.4, Listing 26.5, and Listing 26.23).
c. Best response of "Not Applicable" was reported for subjects without any lesions identified at Baseline and no new lesions at the first assessment.
d. Fisher's exact test.

ORR in subgroups

ORR was analysed for the following subgroups: Primary Efficacy Population without or with prior chemotherapy; ITT population subgroup with V600E mutation or with V600K mutation.

The ORR for patients in the trametinib arm with or without prior chemotherapy was similar. For patients on chemotherapy arm who had received prior chemotherapy the ORR was zero; however, there were a higher percentage of patients with stable disease compared with patients in the chemotherapy arm who had not received prior chemotherapy.

The ORR data by mutation status are described in table 14.

Table 14: Investigator-Assessed Best Confirmed Response in Subjects by Mutation Status (ITT Population MEK114267)

	V600E Mutation		V600K Mutation	
	Trametinib (N=184)	Chemotherapy (N=97)	Trametinib (N=29)	Chemotherapy (N=11)
Best response (RECIST 1.1), n (%)				
Complete response	4 (2)	0	NA	NA
Partial response	40 (22)	7 (7)	3 (10)	2 (18)
Stable disease	97 (53)	32 (33)	22 (76)	2 (18)
Progressive disease	35 (19)	45 (46)	3 (10)	5 (45)
Not evaluable	8 (4)	13 (13)	1 (3)	2 (18)
Response rate, n (%)				
CR+PR	44 (24)	7 (7)	3 (10)	2 (18)
95% CI	(17.9,30.7)	(3.0,14.3)	(2.2,27.4)	(2.3,51.8)
Difference in ORR, n (%)				
Difference (%)	17		-8	
95% CI [a]	(5.5,28.9)		(-49.2,25.9)	
P-value [a]	0.0026		0.6700	

Abbreviations: CI = confidence interval; CR = complete response; NA = not applicable; ORR = overall response rate; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; a. Fisher's exact test.

Duration of Response

Table 15: Median duration of confirmed response by subject population

Analysis Population	Median Duration of Response (months)			
	Investigator Assessed		Independent Review Assessed	
	Trametinib	Chemotherapy	Trametinib	Chemotherapy
n	43	7	52	9
Primary Efficacy	5.5	--	5.6	--
95% CI	(4.9, 5.9)	(3.5,--)	(3.8, 5.9)	(3.5,--)
n	47	9	41	5
ITT	5.5	--	5.6	--
95% CI	(4.1, 5.9)	(5.0,--)	(4.1, 5.9)	(3.5,--)
n	27	7	NA	NA
V600E no brain mets without prior chemotherapy	5.5	--	NA	NA
95% CI	(5.4, 5.9)	(3.5,--)		
n	16	0	NA	NA
V600E no brain mets with prior chemotherapy	4.9	--	NA	NA
95% CI	(3.4,--)	(--,--)		
n	44	7	NA	NA
V600E Mutation	5.5	--	NA	NA
95% CI	(4.9, 5.9)	(3.5,--)		
n	3	--	NA	NA
V600K Mutation	4.1	--	NA	NA
95% CI	(--, --)	(--,--)		

Data Source: Table 7.129, Table 7.130, Table 7.131, Table 7.132, Table 7.133, Table 7.134, Table 7.135, Table 7.136
Abbreviations: CI = confidence interval; NA = not applicable (analysis was not performed), ITT = intent-to-treat; -- = not reached.

SuSummary of main study

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

Table 16: Summary of Efficacy for trial MEK114267

Title: a Phase III randomized, open-label study comparing GSK1120212 to chemotherapy in subjects with advanced or metastatic BRAF V600E/K mutation-positive melanoma		
Study identifier	MEK114267	
Design	Open-label, multicentre, randomised, controlled	
	Duration of main phase:	Study treatments to be continued until the occurrence of disease progression, death or withdrawal.
Hypothesis	Superiority	
Treatments groups	Trametinb (2 mg QD)	214 patients
	Chemotherapy (DTIC or paclitaxel)	108 patients

Endpoints and definitions	Primary endpoint	PFS	defined as the time from randomization until the earliest date of radiological disease progression documented by the investigator per RECIST v1.1 or death due to any cause.
	Secondary endpoint	OS	defined as the time from randomization until death due to any cause.
Database lock	6 January 2012 – updated analysis: 20 May 2013*		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to Treat Population		
Descriptive statistics and estimate variability	Treatment group	Trametinb (2 mg QD)	Chemotherapy (DTIC or paclitaxel)
	Number of subject	214	108
	Investigator assessed Median PFS (months) (95% CI)	4.8 (4.3, 4.9)	1.5 (1.4, 2.7)
	Hazard Ratio (95% CI) Log rank-p-value	0.45 (0.33, 0.63) p<0.0001	
	Independent review assessed Median PFS (months) (95% CI)	4.9 (4.6, 5.0)	1.5 (1.4, 2.8)
	Hazard Ratio (95% CI) Log rank-p-value	0.42 (0.29,0.59) p<0.0001	
	*Median Overall Survival (months) (95%, CI)	15.6 (14.0, 17.4)	11.3 (7.3, 14.8)
	Hazard Ratio (95%, CI)	0.78 (0.57, 1.06) p=0.091	
	Survival at 6 months (%) (95% CI)	81 (73, 86)	67 (55, 77)
	Hazard Ratio (95% CI) Log rank-p-value	0.53 (0.30, 0.94) p=0.0181	
	Independent review assessed response (%) CR PR SD ORR (CR+PR) 95% CI	 0 19% 51% 19% (14.1%, 25.1%)	 <1% 4% 31% 5% (0.7%, 9.0%)
	Difference (95% CI) p-value	15 % (4.6, 25.5) 0.0029	

	Investigator assessed response (%) CR PR SD ORR (CR+PR) 95% CI	 2% 20% 56% 22% (16.6%, 28.1%)	 0% 8% 31% 8% (3.9%, 15.2%)
	Difference (95% CI) p-value	14% (3.1, 25.1) 0.0100	
	Median duration of Response (months) (95% CI)	5.5 (4.1, 5.9)	- (5.0,-)

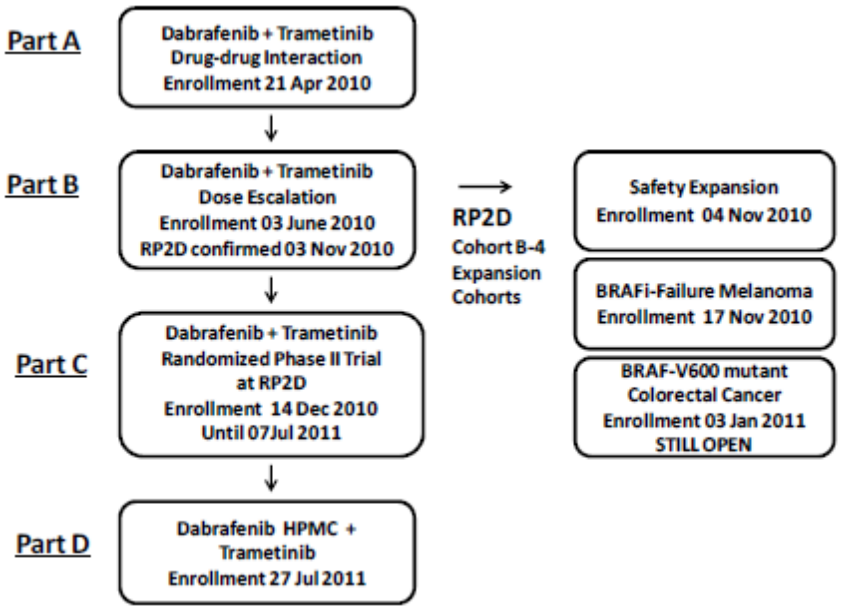
2.5.2.2. Combination therapy:

2.5.2.2.1. Pivotal Study BRF113220

An open-label, dose-escalation, Phase IB/II study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of the BRAF inhibitor GSK2118436 in combination with the MEK inhibitor GSK1120212 in subjects with BRAF mutant metastatic melanoma. Part C of study BRF113220 was considered the pivotal study supporting the application of the combination treatment dabrafenib and trametinib.

Methods

The study comprised 4 parts, of which Parts A, B, and D together constituted the Phase I part, and Part C constituted the randomised Phase II part of the study.



Study Participants

Subjects with BRAF V600 mutation positive melanoma were required for Part D; other BRAF mutation-positive tumour types could be enrolled in Part A and Part B as well with approval of the GSK Medical Monitor.

Subjects with BRAF mutant melanoma who had prior exposure to BRAF inhibitors (BRAFi) or subjects with BRAF mutant colorectal cancer were enrolled to Part B expansion cohorts.

Patients in Part C were required to have an unresectable locally advanced or metastatic melanoma harbouring a BRAF V600 mutation (i.e. V600E, V600K or V600D) and measurable disease according to RECIST criteria.
Patients with prior exposure to BRAF or MEK inhibitors, or prior anti-cancer therapy in the metastatic setting with the exception of up to one regimen of chemotherapy and/or interleukin-2 were excluded. Also, patients with active brain metastases or cardiac comorbidities were excluded.

Treatment

Dabrafenib was taken twice daily, approximately 12 hrs apart. Trametinib was taken once daily. Both drugs were taken orally with approximately 200 mL of water either one hour before or 2 hours after a meal. Subjects were encouraged to take study drug daily at approximately the same times of day.

Patients in part C of study BRF113220 were randomized to 3 arms: dabrafenib 150 mg BID + trametinib 2 mg QD (150/2 combination), dabrafenib 150 mg BID + trametinib 1 mg QD (150/1 combination), and dabrafenib monotherapy at 150 mg BID alone. For the combination treatment dabrafenib 150 mg was taken twice daily orally, approximately 12 hours apart. Trametinib was taken once daily.

Patients who progressed on the dabrafenib monotherapy arm had the opportunity to receive dabrafenib and trametinib (2 mg) in combination dosing upon disease progression.

Objectives and Endpoints

Part A

	Objectives	Endpoints
Primary	To determine the PK of single dose dabrafenib (and its metabolite(s), including hydroxydabrafenib), alone and with repeat dose trametinib dosed orally	Single dose PK parameters for dabrafenib (and its metabolite(s), including hydroxydabrafenib), including maximum observed concentration Cmax, area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration (AUC(0-t)) and extrapolated to infinity (AUC(0-∞))
Secondary	To confirm steady-state exposure of trametinib	Trametinib concentrations during concomitant dabrafenib

Please see clinical pharmacology for further details

Part B

Please see section 2.5.1 for further details

Part C

	Objectives	Endpoints
Primary	To determine clinical activity of dabrafenib and trametinib in subjects with BRAF mutant metastatic melanoma.	Response rate (complete response [CR] + partial response [PR]) of dabrafenib and trametinib in BRAF mutant metastatic melanoma. Duration of response. PFS
	To determine the safety, tolerability and range of tolerated doses of dabrafenib and trametinib dosed orally in combination in subjects with BRAF mutant metastatic melanoma.	AEs (including rate of squamous cell carcinoma) and changes in laboratory values and vital signs
Secondary	To characterize the population PK parameters of dabrafenib and trametinib when administered daily in subjects with BRAF mutant metastatic melanoma.	Population PK parameters, such as oral clearance (CL/F) and oral volume of distribution (V/F) of dabrafenib and trametinib will be determined. Additional PK parameters may also be estimated.
	To characterize the durability of response in subjects achieving clinical benefit.	Overall survival (OS)

Disease assessment included imaging (e.g., CT, MRI, bone scan, plain radiograph) according to RECIST 1.1 criteria, and physical examination (as indicated for palpable superficial lesion). There was no planned adjustment for multiplicity.

Part D

	Objectives	Endpoints
Primary	To determine single dose and steady-state PK of dabrafenib hydroxypropyl-methylcellulose (HPMC) capsules alone and in combination with trametinib dosed orally	Single and steady-state PK parameters for dabrafenib HPMC capsules including Cmax, tmax, AUC(0-t), and AUC(0-∞) (single dose for AUC(0-∞))
	To determine the safety and tolerability of dabrafenib and trametinib dosed orally in combination in subjects with BRAF V600 mutation positive metastatic melanoma	AEs (including rate of squamous cell carcinoma) and changes in laboratory values and vital signs
Secondary	To determine the single dose and steady state PK of dabrafenib metabolites using HPMC capsules	Single dose and steady-state PK parameters for dabrafenib metabolites using HPMC capsules including Cmax, Tmax, AUC(0-t), and AUC(0-∞) (single dose for AUC(0-∞)), if data permit
	To determine single dose and steady-state PK of trametinib	Trametinib single dose and steady state PK parameters including Cmax, tmax, AUC(0-t) during concomitant dabrafenib
	To evaluate clinical activity of the dabrafenib and trametinib combination in subjects with BRAF V600 mutation positive metastatic melanoma	Tumor response as defined by RECIST 1.1. Overall survival.

The following sections will be focusing on Part C of the study.

Sample size

With a sample size of 50 patients for each arm (planned sample size for BRF113220 Part C), for the comparison of each combination treatment to monotherapy trametinib, the study had 82% statistical power to detect an absolute 17% decrease in cuSCC in patients who received the combination dose of dabrafenib and trametinib (pC=3%) compared to patients who received 150 mg two time a day dabrafenib administered alone (pM=20%). The rate of 20% for dabrafenib monotherapy was hypothesized based on Phase I data and published data with vemurafenib. Fisher's exact test was utilized in the calculations, and a nominal type I error rate of 0.05 was assumed.

The sample size calculation was not based on the primary endpoints (PFS, ORR, DoR), which underlines that this phase I/II trial was not planned to provide confirmatory evidence on the efficacy of the combination. This is also clear from the more serious fact that no confirmatory testing strategy was planned. A total of 162 patients were enrolled.

Randomisation

Patients in BRF113220 Part C were assigned with a 1:1:1 ratio to study treatment (150/2 combination, 150/1 combination or 150 mg dabrafenib alone) in accordance with the randomization schedule generated by Discovery Biometrics, prior to the start of the study, using validated internal software. Patients were not stratified for key prognostic variables.

Blinding (masking)

This was an open-label study. The assessment of the efficacy results is based on investigator assessment and blinded independent central review (BICR). In addition, independent review by ECHO was also conducted.

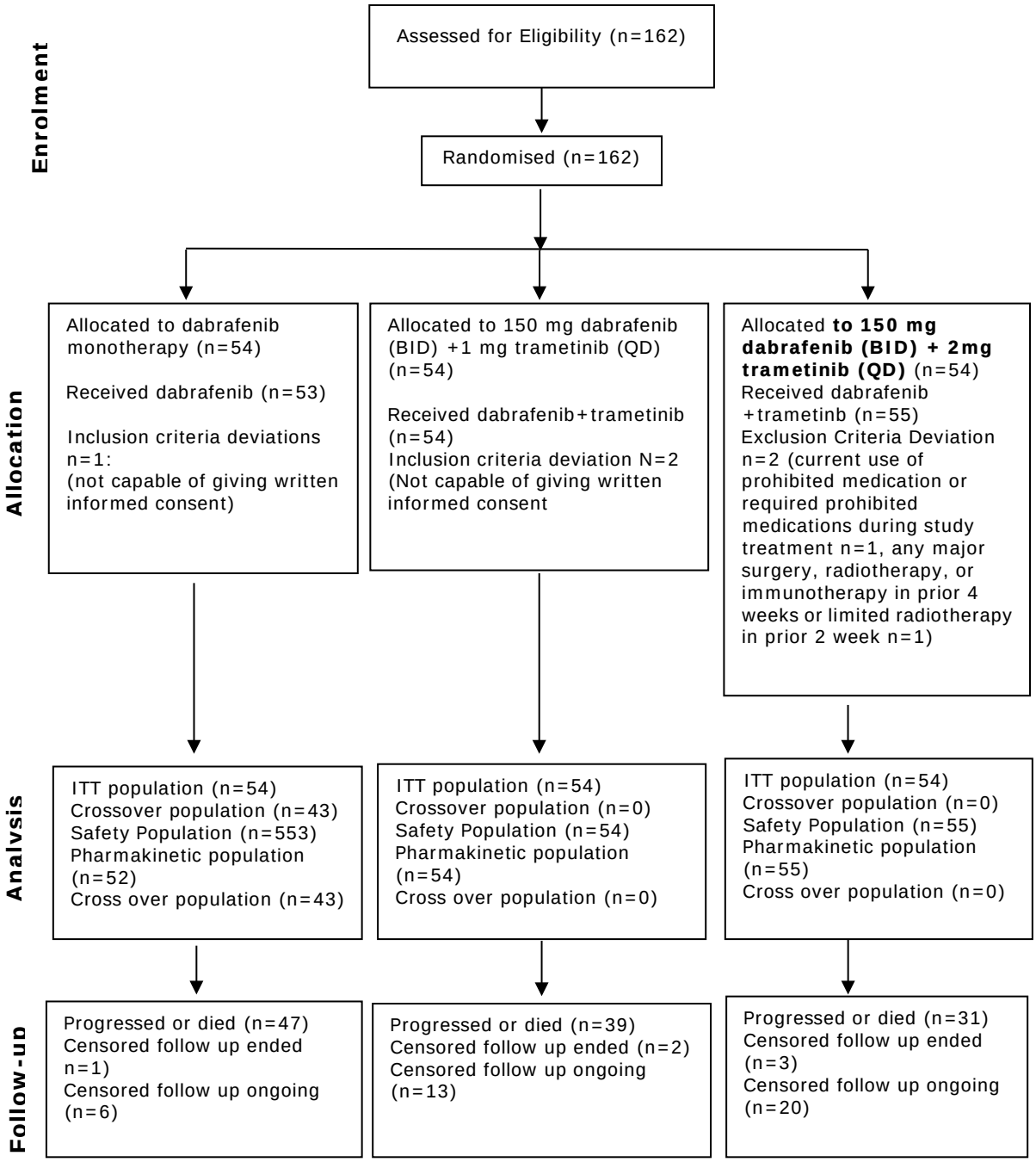
Statistical methods

Comparisons of each of the combination arms vs the monotherapy arm were planned for each of the primary endpoints. PFS was censored for symptomatic progression without scan-evidence, start new therapy with scan-evidence of progression, and PD or death after more than two visits.. Eight sensitivity analyses were planned to investigate the robustness of PFS against these censoring rules and possible discrepancy between PFS by blinded independent review vs PFS.

One efficacy interim analysis was planned when 75 patients across the three treatment arms had completed at least three post-dose disease assessments.

Results

Participant flow



Recruitment

The first subject was screened on 26 Mar 2010. The clinical data cut-off for Parts A, B, and D of the study was 25 May 2012, and for Part C was 31 May 2012.

Conduct of the study

Part C was initially designed as non-randomized expansion cohorts based on doses identified in Part B, with enrolment of approximately 20 patients per dose cohort. A pre-specified interim analysis of Part C safety and efficacy data by treatment arm was conducted. Based on the discussion of the results of the interim analysis with health authorities the protocol was amended; sample size was increased, a randomization procedure and a dabrafenib monotherapy arm were added, a Blinded Independent Central Review (BICR) was introduced and several sensitivity analyses were pre-specified for the final analysis in order to facilitate a more robust evaluation of safety and tolerability of the combination. Furthermore OS was included as a secondary endpoint.

The amendments for randomization and sample size increase were implemented before start of recruitment and therefore this strategy was not driven by trial results.

Baseline data

Table 17: Demographics and Baseline Disease Characteristics (ITT Population BRF113220 part C)

	Treatment Groups			Total (All Dose Groups)
Dabrafenib	150 mg BID	150 mg BID	150 mg BID	
Trametinib	--	1 mg QD	2 mg QD	
N	54	54	54	162
Age, y				
Mean (SD)	51.8 (15.19)	49.9 (14.70)	55.9 (11.85)	52.5 (14.13)
Median (Min – Max)	49.5 (18 – 82)	49.0 (23 – 85)	57.5 (27 – 79)	53.0 (18 – 85)
Age Group (y), n (%)				
<65	42 (78)	46 (85)	43 (80)	131 (81)
≥65	12 (22)	8 (15)	11 (20)	31 (19)
<75	51 (94)	51 (94)	52 (96)	154 (95)
≥75	3 (6)	3 (6)	2 (4)	8 (5)
Sex, n (%)				
Female	25 (46)	24 (44)	20 (37)	69 (43)
Male	29 (54)	30 (56)	34 (63)	93 (57)
ECOG PS at Baseline, n (%)				
ECOG 0	34 (63)	38 (70)	35 (65)	107 (66)
ECOG 1	20 (37)	16 (30)	19 (35)	55 (34)
BRAF Mutation Status, n (%)				
V600E	45 (83)	45 (83)	47 (87)	137 (85)
V600K	9 (17)	9 (17)	7 (13)	25 (15)
Primary Tumor Type at Initial Diagnosis, n (%)				
Melanoma	53 (98)	53 (98)	54 (100)	160 (99)
Unknown	1 (2)	1 (2)	0	2 (1)
Stage at Screening, n (%)				
IIIc[a]	1 (2)	1 (2)	0	2 (1)
IV	53 (98)	53 (98)	54 (100)	160 (99)
(M Stage) at Screening, n (%)				
M0[a]	1 (2)	1 (2)	0	2 (1)
M1a	11 (20)	9 (17)	6 (11)	26 (16)
M1b	5 (9)	11 (20)	10 (19)	26 (16)
M1c	37 (69)	33 (61)	38 (70)	108 (67)
Baseline LDH, n (%)				
≤ULN	27 (50)	29 (54)	32 (59)	88 (54)
>ULN	27 (50)	25 (46)	22 (41)	74 (46)
Prior history of Brain Metastases, n (%)				
No	50 (93)	47 (87)	52 (96)	149 (92)
Yes	4 (7)	7 (13)	2 (4)	13 (8)
Number of Disease Sites at Baseline, n (%)				
≥3 Sites	34 (63)	27 (50)	28 (52)	89 (55)
<3 Sites	20 (37)	27 (50)	26 (48)	73 (45)

Prior anti-cancer treatment

Table 18: Prior Anti-Cancer Therapy (ITT Population BRF113220 part C)

	Treatment Groups			Total (All Dose Groups)
Dabrafenib	150 mg BID	150 mg BID	150 mg BID	
Trametinib	--	1 mg QD	2 mg QD	
N	54	54	54	162
Any Therapy[a], n (%)	**53 (98)**	**50 (93)**	**53 (98)**	**156 (96)**
Surgery	53 (98)	50 (93)	53 (98)	156 (96)
Radiotherapy	14 (26)	13 (24)	20 (37)	47 (29)
Immunotherapy	8 (15)	16 (30)	13 (24)	37 (23)
Chemotherapy (cytotoxics, non-cytotoxics)	12 (22)	15 (28)	7 (13)	34 (21)
Biologic therapy (mAbs, vaccines)	11 (20)	9 (17)	12 (22)	32 (20)
Small molecule targeted therapy	0	1 (2)	1 (2)	2 (1)
Unknown	1 (2)	0	0	1 (<1)
Number of Prior Advanced or Metastatic Regimens, n (%)				
0	47 (87)	42 (78)	42 (78)	131 (81)
1	4 (7)	10 (19)	11 (20)	25 (15)
2[b]	3 (6)	1 (2)	0	4 (2)
3[b]	0	1 (2)	0	1 (<1)
4[b]	0	0	1 (2)	1 (<1)
Number of Chemotherapy Regimens in Advanced or Metastatic Setting, n (%)				
0	50 (93)	45 (93)	48 (89)	143 (88)
1	4 (7)	7 (13)	6 (11)	17 (10)
2	0	2 (4)	0	2 (1)
Number of Immunotherapy or Biologic Regimens in Advanced or Metastatic Setting, n (%)				
0	50 (93)	46 (85)	47 (87)	143 (88)
1	3 (6)	7 (13)	6 (11)	16 (10)
2	1 (2)	1 (2)	0	2 (1)
4	0	0	1 (2)	1 (<1)

Abbreviations: BID=Two times a day; mAb=Monoclonal antibody; QD=Once daily.
Note: If a subject was missing the regimen number, it was assumed to be 1 separate regimen.
a. No subjects reported any prior hormonal anti-cancer therapy.

b. Six subjects received prior anti-cancer regimens that could not be easily classified as advanced or metastatic

According to the baseline characteristics of BRF113220 study, an imbalance in percentage of patients receiving previous chemotherapy is observed.

Numbers analysed

All 162 randomised subjects were included in the ITT population.

Table 19: Analysis population

	Treatment Groups			Total (All Dose Groups)
Dabrafenib	150 mg BID	150 mg BID	150 mg BID	
Trametinib	--	1 mg QD	2 mg QD	
All Treated Population	53	54	55[a]	162
ITT Population	54[a]	54	54	162
Crossover Population	43	0	0	43
Pharmacokinetic Population	52	54	55	161

Data Source: Table 9.1
Abbreviations: BID=Two times a day; QD=Once daily.
a. Subject 1061 was randomized to receive dabrafenib monotherapy but instead received only 150/2 combination therapy, and is therefore included in the all treated population for the 150/2 combination therapy group (having received this treatment)for safety and in the ITT population for the monotherapy group (having been randomized to this group) for efficacy.

Outcomes and estimation

PFS

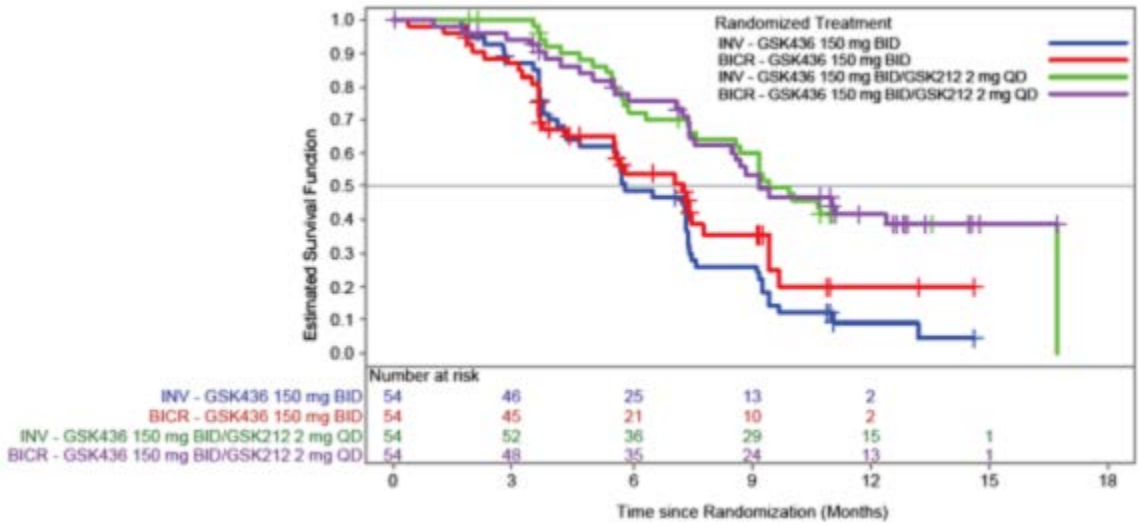
According to the investigators treatment with 150/2 combination therapy resulted in a statistically significant improvement in investigator-assessed PFS compared to treatment with dabrafenib monotherapy, with a HR of 0.39 (95% CI: 0.25- 0.62; p<0.0001). The median PFS was 9.4 months for patients treated with 150/2 combination therapy and 5.8 months for patients treated with dabrafenib monotherapy. A Kaplan-Meier estimate of PFS rate showed in the 150/2 combination group a proportion of 41% of the patients remaining progression-free at 12 months compared with 9% with dabrafenib monotherapy. Likewise, treatment with 150/1 combination therapy resulted in a statistically significant improvement in investigator-assess PFS compared to treatment with dabrafenib monotherapy, with an HR of 0.56 (95% CI: 0.37- 0.87, p=0.0057).

Results from Blinded Independent Central Review are summarised in the below table.

Table 20: Kaplan-Meier Estimates of BICR-Assessed PFS (ITT Population BRF113220 Part C)

	Treatment Groups		
Dabrafenib	150 mg BID	150 mg BID	150 mg BID
Trametinib	--	1 mg QD	2 mg QD
N	54	54	54
Number of Subjects, n (%)			
Progressed or died (event)	32 (59)	36 (67)	28 (52)
Censored, follow-up ended	17 (31)	6 (11)	6 (11)
Censored, follow-up ongoing	5 (9)	12 (22)	20 (37)
Hazard Ratio[a]			
Estimate (95% CI)	--	0.73 (0.45, 1.19)	0.54 (0.32, 0.91)
Log rank p-value	--	0.1721	0.0121
Estimates, months[b]			
1st Quartile (95% CI)	3.7 (3.2, 5.6)	3.8 (3.6, 5.6)	7.1 (4.6, 8.5)
Median (95% CI)	7.3 (5.5, 9.4)	8.3 (5.6, 11.3)	9.2 (7.6, -)
3rd Quartile (95% CI)	9.7 (7.5, -)	14.8 (11.1, -)	- (12.4, -)

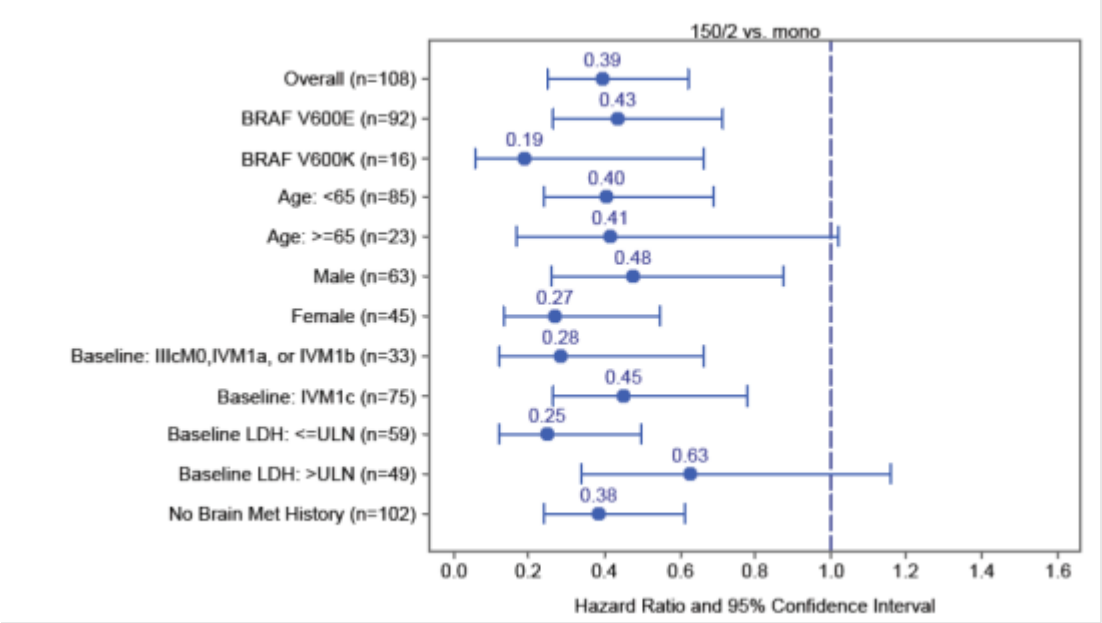
Abbreviations: BID=Two times a day; CI=Confidence interval; QD=Once daily.
Note: P-values are based on 2-sided log rank test. The censoring method included censoring for extended loss to follow-up, new anti-cancer therapy, and excluding symptomatic progression.
a. HRs were estimated using the Pike estimator. A HR <1 indicates a lower risk with this treatment compared with the monotherapy group. Confidence intervals were estimated using the Brookmeyer Crowley method.



Abbreviations: INV=Investigator-assessed; BICR=Blinded Independent Central Review.

Figure 6: Investigator- and BICR-Assessed Kaplan-Meier Curves for PFS (dabrafenib mono vs 150.2) (ITT Population BRF113220 part C)

Investigator-assessed PFS in subgroups



Abbreviations: LDH=Lactate dehydrogenase; Met=Metastases; ULN=Upper limit of normal.

Figure 7: Forrest Plots for PFS in subgroups (150/2 Combination Therapy vs. Dabrafenib Monotherapy study BRF113220 part C)

Overall Survival

With a median follow-up time of 14 months and a total of 51 deaths in the study, OS data are not yet mature and median OS has not been reached on any treatment group.

The Kaplan-Meier estimates of OS at 12 months was 79% (95%CI: 66, 88) for 150/2 combination therapy, compared with 68% (95% CI: 54, 79) for 150/1 combination therapy and 70% (95% CI: 55, 80) for dabrafenib monotherapy. The OS estimates for the monotherapy group includes patients who crossed over (81% of randomized monotherapy patients).

Table 21: Overall Survival and 12-Month Estimated Survival Rates (ITT Population BRF113220 part C)

	Treatment Groups		
Dabrafenib	**150 mg BID**	**150 mg BID**	**150 mg BID**
Trametinib	**--**	**1 mg QD**	**2 mg QD**
N	**54**	**54**	**54**
Subject Classification, n (%)			
Died (event)	19 (35)	18 (33)	14 (26)
Censored, follow-up ended	0	4 (7)	0
Censored, follow-up ongoing	35 (65)	32 (59)	40 (74)
Hazard Ratio[a]			
Estimate (95% CI)	--	0.98 (0.51, 1.87)	0.67 (0.34, 1.34)
Log rank p-value	--	0.9514	0.2591
Kaplan-Meier Estimates for Overall Survival, months[b]			
1st Quartile (95% CI)	10.7 (7.9, 13.4)	10.3 (9.1, -)	12.7 (9.6, -)
Median (95% CI)	- (13.4, -)	- (14.5, -)	- (-, -)
3rd Quartile (95% CI)	- (-, -)	- (-, -)	- (-, -)
Estimated Survival at 12 Months, %			
Rate (95% CI)	70 (55, 80)	68 (54, 79)	79 (66, 88)

Abbreviations: BID=Two times a day; CI=Confidence interval; QD=Once daily.
Note: P-values are based on 2-sided log rank test. Monotherapy group includes data from the crossover phase.
a. HRs are estimated using the Pike estimator. A HR <1 indicates a lower risk with this treatment compared with themonotherapy group. b. CIs were estimated using the Brookmeyer Crowley method.

During the procedure, the Applicant submitted an overall survival analysis based upon the March 2013 data cut-off of BRF113220. As of this data cut-off, 51% of patients had died (83/162) across all three arms and the median follow-up was 24 months.

Eighty three percent (83%) of the dabrafenib monotherapy population crossed over to 150/2 upon disease progression, and the additional time on combination is counted in the randomized monotherapy treatment summaries.

Table 22: Survival Data summaries from the Primary and posthoc analyses

Cut-off dates	Treatment	Number of deaths (%)	Median months	Hazard Ratio (95% CI)
May 31, 2012[1]	Dabrafenib	19 (35)	NR (13.4.4, NR)	
	150/1 Combination	18 (33)	NR (14.5, NR)	0.98 (0.51, 1.87)
	150/2 Combination	14 (26)	NR (NR, NR)	0.67 (0.34, 1.34)
March 29, 2013[2]	Dabrafenib	31 (57)	20.2 (14.5, 25.9)	
	150/1 Combination	27 (50)	18.7 (13.7, NR)	0.96 (0.57,1.60)
	150/2 Combination	25 (46)	23.8 (17.5, NR)	0.73 (0.43,1.24)

Notes:
1. BRF113220 Part C CSR Table 21; Source Tables 12.71 (m5.3.5.1)
2. BRF113220 Safety Update Table 12.71

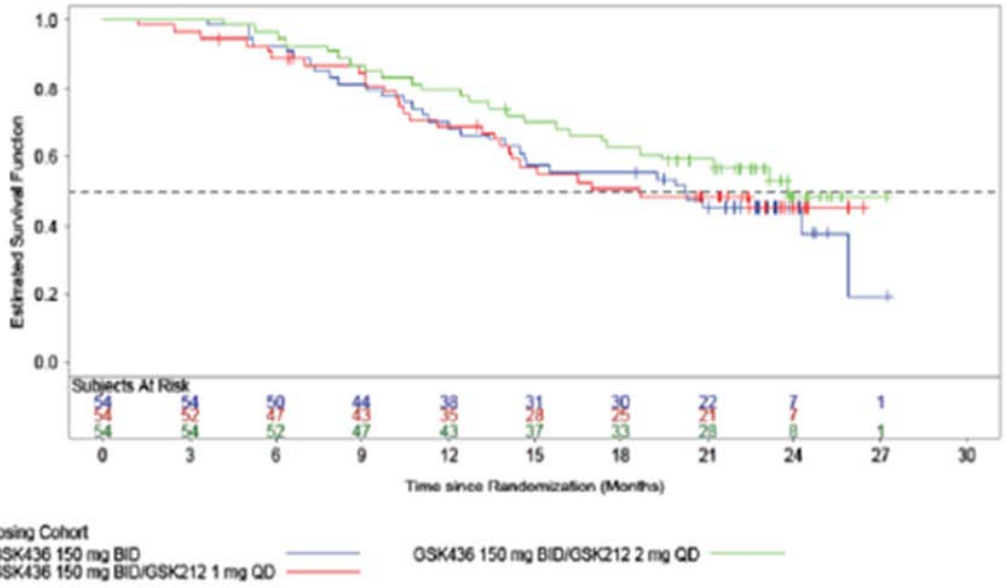


Figure 8: Overall Survival Kaplan Meier Curves Based on 29 March 2013 data

ORR

Independent assessment (BICR analysis) showed that the 150/2 combination group resulted in a higher ORR compared to dabrafenib monotherapy, although the difference was not statistically significant. BICR-assessed confirmed ORRs for both the 150/2 and 150/1 combination therapy groups were lower than the investigator-assessed rates. The BICR-assessed confirmed ORR was 61% (95% CI; 46.9%- 74.1%) for the 150/2 combination group compared with 46% (95% CI: 32.6%, 60.4%) for the dabrafenib monotherapy group. Ten patients (6%) from all 3 treatment groups had responses classified as "Non-CR/Non-PD", because the BICR could not find target lesions and thus, could not assess if these patients had PRs.

The ORR analysis does not show a benefit of the 150/1 combination when compared to dabrafenib monotherapy.

Duration of response

The duration of the response to dabrafenib monotherapy and the combination regimen in BFR113220, as assessed by Blinded Independent Central Review, show an equal result for the combination 150/2 as well as the monotherapy dabrafenib (150 mg DQ): median DoR 7.6 months. The combination 150/1 shows median DoR of 11.3 months).

Cross-over Phase Efficacy Results - Investigator-assessed ORR

The best confirmed ORR in the crossover phase was 9% (95% CI: 2.6, 22.1), with 47% of the patients achieving SD and 37% having an assessment of PD.

Among the patients who crossed over, PRs were only observed in patients who had either CRs, or PRs while on dabrafenib monotherapy. The ORR in this subgroup of patients was 17% (95% CI: 4.7, 37.4). All the four patients who had PRs after crossover received more than 6 months of dabrafenib monotherapy before crossing over to combination therapy.

Many patients in BRF113220 that encountered PD have received next line treatment and the resulting effectiveness is reflected in the overall disappointing response rate.

As stated, it is nevertheless remarkable that a response of the combination regimen 150/2 could be observed after having had progressive disease (i.e. resistance) during the prior treatment with dabrafenib monotherapy.

Summary of main study

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

Table 23: Summary of Efficacy for trial BRF113220

Title: An open-label, dose-escalation, Phase IB/II study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of the BRAF inhibitor GSK2118436 in combination with the MEK inhibitor GSK1120212 in subjects with BRAF mutant metastatic melanoma.	
Study identifier	BRF113220 part C
Design	Open-label, multicentre, randomised, dose-escalation

	Duration of main phase:		Study treatments to be continued until the occurrence of disease progression, intercurrent illness, pregnancy, unacceptable toxicity, withdrawal of consent. Treatment could be continued after disease progression if the patient was considered to be deriving clinical benefit.
Hypothesis	Exploratory: specify		
Treatments groups	Dabrafenib 150 mg BID		54 patients
	Dabrafenib 150 mg BID + Trametinib 1 mg QD		54 patients
	Dabrafenib 150 mg BID + Trametinib 2 mg QD		54 patients
Endpoints and definitions	Primary endpoint	PFS	defined as the interval of time between the date of randomization and the earlier of date of disease progression or date of death due to any cause
	Secondary endpoint	OS	defined as the interval of time between the date of randomization and the date of death due to any cause.
Database lock	31 May 2012		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Dabrafenib (150 mg BID)	Dabrafenib (150 mg BID) and trametinib (1 mg QD)	Dabrafenib (150 mg BID) and trametinib (2 mg QD)
	Number of subject	54	54	54
	BICR Median PFS (months) (95% CI)	7.3 (5.5, 9.4)	8.3 (5.6, 11.3)	9.2 (7.6, -)
	Hazard Ratio (95% CI) Log rank-p-value		0.73 (0.45, 1.19) 0.1721	0.54 (0.32, 0.91) 0.0121
	Median Overall Survival cut/off date March 29, 2013	20.2 (14.5, 25.9)	18.7 (13.7, NR)	23.8 (17.5, NR)
	Hazard Ratio (95%, CI)		0.96 (0.57, 1.60)	0.73 (0.43, 1.24)
	Survival at 12 months (95% CI)	70 (55, 80)	6 (54, 79)	79 (66, 88)
	Hazard Ratio (95% CI) Log rank-p-value		0.98 (0.51, 1.87) 0.9514	0.67 (0.34, 1.34) 0.2591

	BICR assessed Response (%) CR PR SD ORR (CR+PR) 95% CI	 7 39 37 46 (32.6, 60.4)	 7 31 48 39 (25.9, 53.1)	 13 48 24 61 (46.9, 74.1)
	Difference (95% CI) p-value		-7% (-26.7, 12.3) 0.5008	15% (-5, 33.7) 0.1486
	BICR assessed Median Duration of response (months) (95% CI)	7.6 (5.5,-)	11.3 (6.2,-)	7.6 (6.9,-)

2.5.2.2.2. Phase III study MEK115306 – headline results

Study design

Study MEK115306 is a multi-centre, multi-national, randomized, double-blind, active-controlled phase III trial comparing dabrafenib 150 mg BID + trametinib 2 mg OD versus dabrafenib 150 mg BID + placebo as first line therapy in patients with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma. A total of 423 patients have been randomized (1:1) to receive either dabrafenib 150 mg BID + trametinib 2mg OD or dabrafenib 150 mg BID + placebo. Randomization was stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) versus ≤ ULN) and BRAF mutation (V600E vs V600K).

An external independent Data Monitoring Committee (DMC) monitored the conduct of the study, periodically assessed safety information, and also reviewed efficacy data at the time of the final PFS/interim OS analyses. The Applicant states that the study fully adhered to the principles outlined in the "Guidelines for Good Clinical Practice (GCP)" International Conference on Harmonisation (ICH) Tripartite Guideline, or with local law.

The primary objective of the MEK115306 study was to show superiority of the combination dabrafenib-trametinib versus dabrafenib-placebo in terms of Progression Free Survival (PFS), according to investigator assessment. Secondary objectives included Overall Survival (OS), overall tumour response rate (ORR), 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 subject who achieve an overall response), safety and pharmacokinetics. Exploratory objectives were evaluation of health related quality of life (according to EORTC QLQ-C30 and EQ-5D questionnaires) and pharmacogenomics. A PFS analysis according to a blinded independent review committee (BIRC) according to RECIST 1.1 criteria was performed as a sensitivity analysis.

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 the medical monitor if they had achieved an objective (partial or complete) response or had imaging evidence of tumour reduction lasting at least 8 weeks. Moreover, cross-over from the dabrafenib-placebo arm to the combination arm was not allowed.

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 randomisation ratio of 1:1 a total of 155 events (progression or deaths) were estimated to be required. According to the statistical analysis 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 had died or was lost to follow-up.

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%.

Baseline characteristic patients in MEK115306

In order to be eligible for the study, patients were required to have histologically confirmed cutaneous melanoma stage IIIc or IV with a BRAF V600E or K mutation as centrally assessed according to the bioMerieux THxID BRAF Assay, measurable disease according to RECIST criteria, ECOG PS 0 or 1. Prior treatment with a BRAF or MEK inhibitor, as well as prior systemic treatment (with exclusion of adjuvant therapy) was not allowed. Adjuvant treatment with ipilimumab must be ended at least 8 weeks prior to randomisation. Patients with brain metastases were allowed to participate if asymptomatic without use of neither corticosteroids nor enzyme inducing anticonvulsivants and radiographically stable for at least 12 weeks prior to randomisation. Exclusion criteria consisted also of history or evidence or predisposing factors for retinal vein occlusion or central serous rethinopathy.

Table 24: Demographic characteristics for 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 25: Baseline Disease Characteristics for 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 26: Stratification Factors in 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)

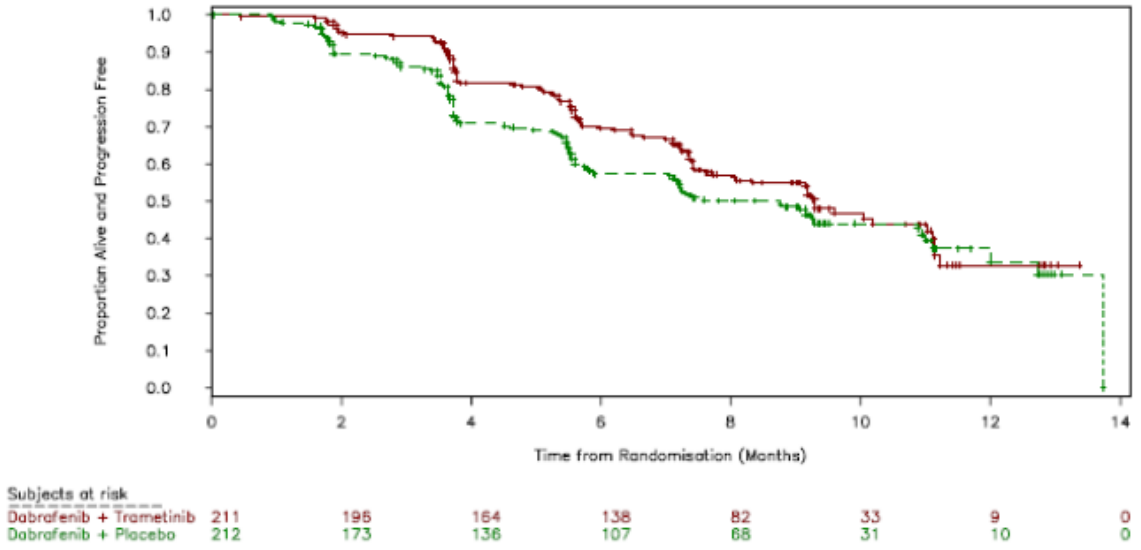
Progression-Free Survival

The MEK115306 PFS data are shown in the Table and Figure below.

Table 27: PFS by investigator and BIRC assessment for MEK115306

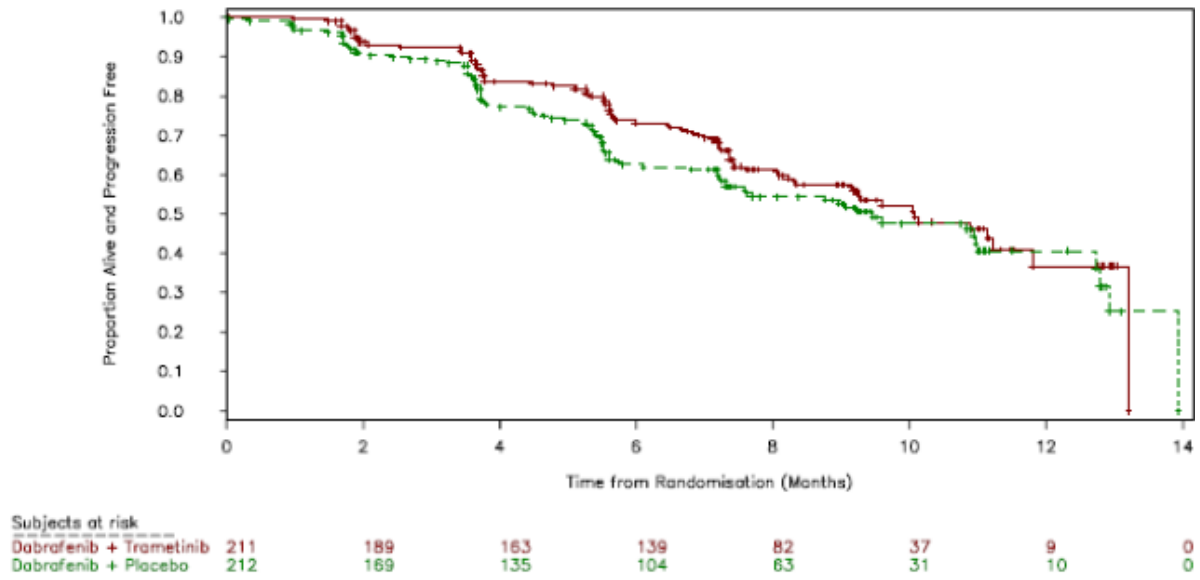
	Investigator Assessment		BIRC Assessment	
	Dabrafenib+ Trametinib (N=211)	Dabrafenib+ Placebo (N=212)	Dabrafenib+ Trametinib (N=211)	Dabrafenib+ Placebo (N=212)
Number of subjects				
Progressed or died (event)	102 (48)	109 (51)	93 (44)	94 (44)
Censored, follow-up ended	14 (7)	22 (10)	24 (11)	40 (19)
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	

MEK115306 Table 2.1010



MEK115306 Figure 12.0010

Figure 9: Kaplan-Meier analysis for investigator assessment of PFS for MEK115306



MEK115306 Figure 12.0050

Figure 10: Kaplan-Meier analysis for BIRC assessment of PFS for MEK115306

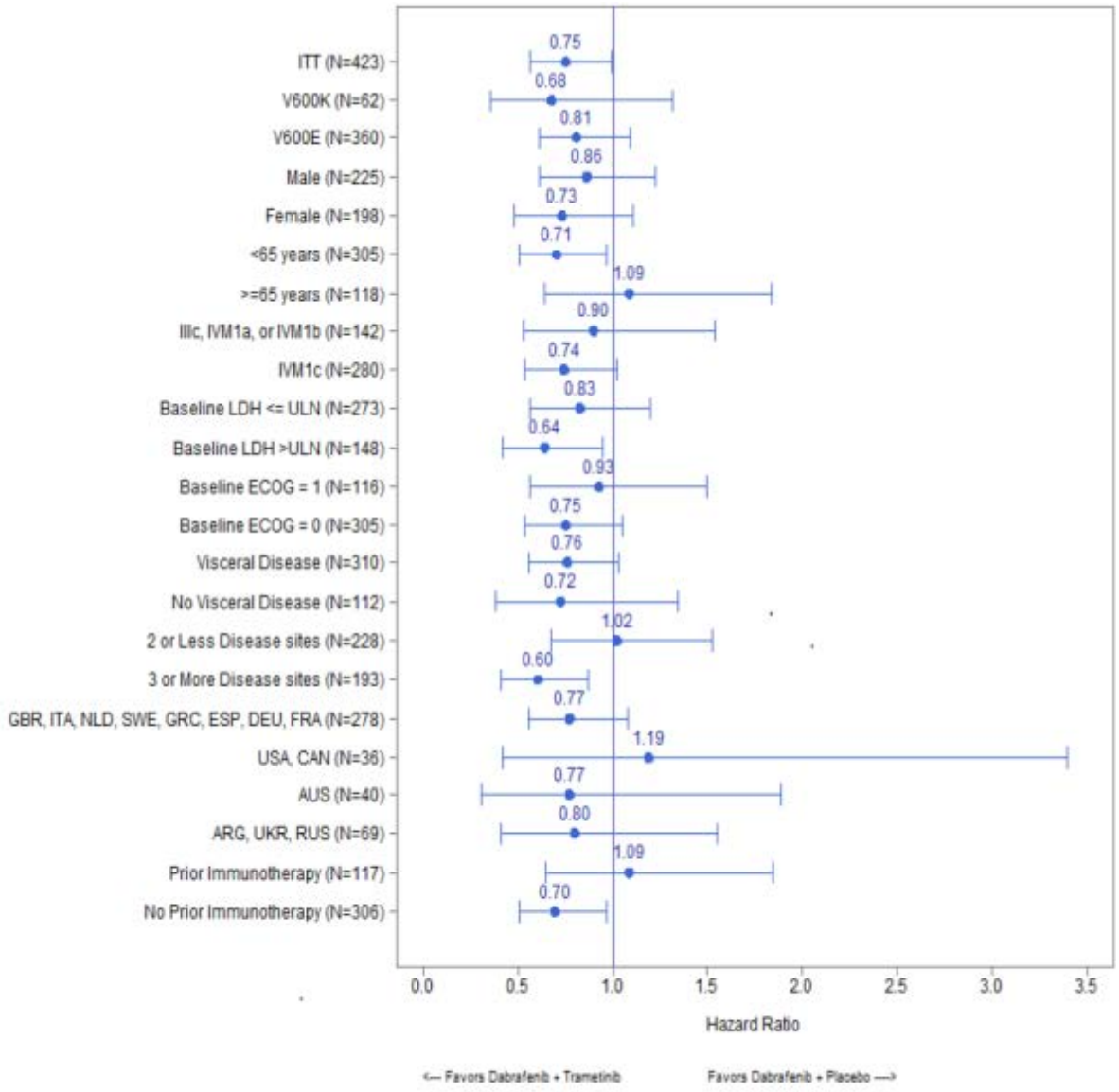
A stepwise Cox model was created, using a 0.05 p-value cutoff for inclusion in the model (Table 28). The final model included gender, visceral disease, and disease stage. After adjusting for these factors, the hazard ratio for treatment remained at 0.75 with a p-value of 0.04.

Table 28: Summary of COX proportional hazards regression model for investigator-assessed PFS

N/n	Covariate	Effect tested	Hazard ratio[b]	95% CI	P-value[a]
423/421[a]	Treatment	Dabrafenib +Trametinib/ Dabrafenib + Placebo	0.75	(0.57, 0.99)	0.040
	Stage at screening	IVM1c/IIIc, IVM1a, or IVM1b	1.75	(1.27, 2.41)	<0.001
	Visceral disease	No/Yes	0.64	(0.44, 0.91)	0.014
	Sex	F/M	0.73	(0.55, 0.96)	0.026

a. N/n: Population/Subjects with data available for all covariates.
b. For each covariate, a hazard ratio <1 indicates a lower risk on the first effect tested compared with the other effects tested
c. Wald chi-squared test is used to calculate the p-value.
d. MEK115306 Table 2.1070

In study MEK115306, PFS analysis by investigator assessment was based on events in half of patients (combination: 102 events, 48%; monotherapy: 109 events, 51%).



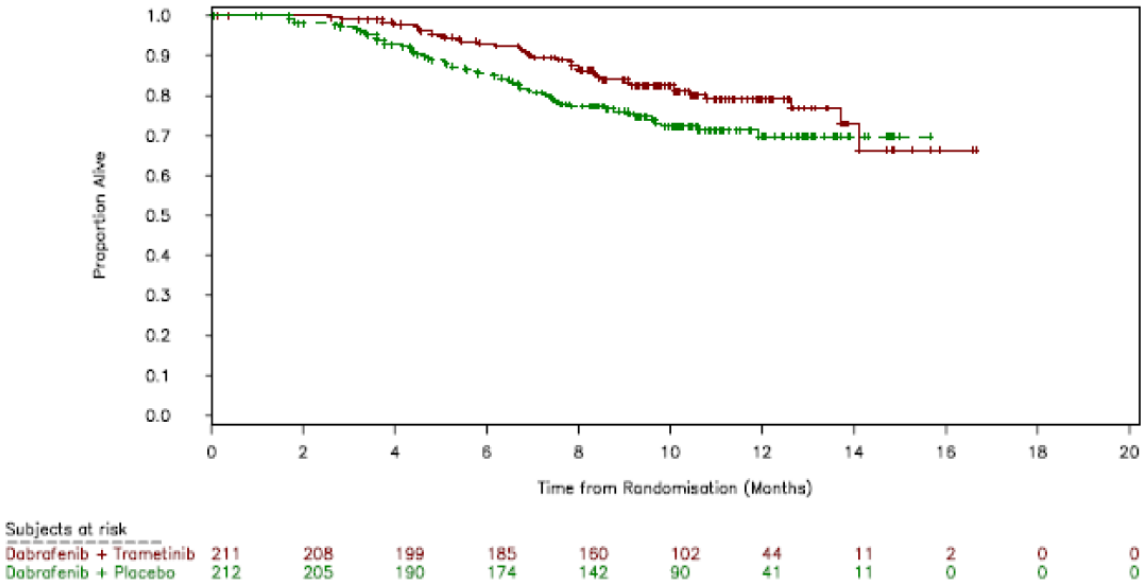
1. MEK115306 Figure 12.2013

Figure 11: Forrest Plots for PFS in subgroups (combination Therapy vs. dabrafenib monotherapy study MEK115306)

Overall survival

At the time of the final PFS analysis, an interim analysis of OS was performed as specified in the protocol. The final analysis of OS is planned when 70% of the total enrolled population has died or been lost to follow up. The data presented below are based on an August 26, 2013 data cut-with 211 (50%) PFS events and 95 (22%) OS events. Events for the final analysis of OS are projected for Q1 2015.

The planned interim analysis of Overall Survival occurred at a time when 95 patients had died (40 in the combination arm and 55 in the monotherapy arm). With a median follow-up time of approximately 9 months on each arm, the median OS point estimate have not yet been reached.



1. MEK115306 Figure 12.1010

Figure 12: Kaplan-Meier analysis of OS for MEK115306

Table 29: Analysis of OS for MEK115306

	Dabrafenib + Trametinib (N=211)	Dabrafenib + Placebo (N=212)
Number of subjects		
Died (event)	40 (19)	55 (26)
Censored, follow-up ended	17 (8)	10 (5)
Censored, follow-up ongoing	154 (73)	147 (69)
Estimates for overall survival(months)		
1st quartile (95% CI)	13.7 (10.1, NR)	9.2 (7.1, NR)
Median (95% CI)	NR (14.1, NR)	NR (NR,NR)
3rd quartile (95% CI)	NR (NR, NR)	NR (NR,NR)
Adjusted hazard ratio		
Estimate	0.63	
95% CI	(0.42, 0.94)	
Stratified log-rank p-value	0.023	

NR=not reached

MEK115306 Table 2.2010

Overall Response Rate

Table 30: Response rate by investigator and BIRC assessment in MEK115306 (subjects with measurable disease at baseline by INV assessment)

	Investigator Assessment		BIRC Assessment	
	Dabrafenib + Trametinib (N=210)	Dabrafenib + Placebo (N=210)	Dabrafenib + Trametinib (N=210)	Dabrafenib + Placebo (N=210)
Best response				
Complete response	22 (10)	18 (9)	26 (12)	28 (13)
Partial response	118 (56)	90 (43)	103 (49)	70 (33)
Stable disease	54 (26)	69 (33)	44 (21)	59 (28)
Non-PR/Non-PD	--	--	10 (5)	16 (8)
Progressive disease	13 (6)	19 (9)	16 (8)	16 (8)
Not evaluable	3 (1)	14 (7)	3 (1)	15 (7)
Not applicable	--	--	8 (4)	6 (3)
Response rate				
CR+PR	140 (67)	108 (51)	129 (61)	98 (47)
95% confidence interval	(59.9, 73.0)	(44.5, 58.4)	(54.5, 68.0)	(39.8, 53.7)
Difference in response rate				
CR+PR	15%		15%	
95% CI for difference	(5.9%, 24.5%)		(5.3%, 24.2%)	
P-value	0.0015		0.0024	

MEK115306 Table 2.3010

Clinical studies in special populations

Trametinib has not been studied in children (< 18 years) or in pregnant or lactating women. More than 99% of patients enrolled in the studies performed with Trametinib to date were whites, therefore data are lacking in patients with other races (e.g., blacks, Asians, etc.).

The lack of efficacy data in certain populations, like paediatric patients, pregnant or lactating women, patients with race other than white, are adequately reflected in the SmPC.

No data is available with trametinib in patients with severe renal impairment and moderate or severe hepatic impairment. The SmPC recommends that trametinib in these patients is used with caution.

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

Due to differences in patient populations (e.g. number of prior treatment regimens and histological subtype), study designs (including differences in assessment schedule for PFS), and endpoints, efficacy data have not been integrated.

Table 31: Median OS and HR for trametinib, vemurafenib, and dabrafenib in the phase II and pivotal phase III studies

Agent	Phase	Treatment (Number of Subjects)	mOS (months) (95% CI)	HR (95% CI)	Cross-over	Median Follow-up (months)	Reference
Trametinib	Phase III (MEK114267)	DTIC /Paclitaxel (n=108)	11.3 (7.2, 14.8)	0.78 (0.57, 1.06) p=0.091	65%	8.7	GSK Data as of 20 May 2013[3]
		Trametinib (n=214)	15.6 (14.0, 17.4)			14.7	
	Phase II (MEK113583)	Trametinib (n= 57)	14.3 (11.3, 24.4)	N/A	N/A	13.8	GSK Data as of 04Apr 2013[4]
Vemurafenib	Phase III (BRIM-3)	DTIC (n=338)	10.3 (Not Available)	0.76 (0.63, 0.93) p<0.01	25%	9.45	Chapman, 2012[2]
		Vemurafenib (n=338)	13.6 (12, 15.2)			12.45	
	Phase II (BRIM-2)	Vemurafenib (n=132)	15.9 (11.6, 18.3)	N/A	N/A	12.9	Sosman, 2012[1]
Dabrafenib	Phase III (BRF113683)	DTIC (n=63)	15.6 (12.7, NR)	0.76 (0.48, 1.21)	57%	12.7	GSK Data as of 18 Dec 2012[5]
		Dabrafenib (n=187)	18.2 (16.6, NR*)			15.2	
	Phase II (BRF113710)	Dabrafenib (n=92)	13.1(V600E) (10.4, NR) 12.9(V600K) (6.9, 17.1)	N/A	N/A	11.9	GSK Data as of 30 Apr 2012[6]

Notes:
NR=Not reached; N/A=Not applicable

1. Sosman JA *et al*., 2012
2. Chapman PB *et al*., 2012
3. MEK114267 OS Update Tables 7.30, 7.116 (follow up), 7.117 (crossover)
4. MEK113583 OS Update Table 13.2 and Table 10.78 (04APR2013)
5. BRF113683 OS Update Table 7.2001, 6.7001, (18 Dec 2012)
6. BRF113710 OS Update 7.18, 7.19, 6.999 (30 Apr 2012)

Table 32: Median PFS and HR for trametinib, vemurafenib, and dabrafenib in the pivotal phase III studies

Agent	Study	Treatment (Number of Subjects)	mPFS (months) (95% CI)	HR (95% CI)	Reference
Trametinib	MEK114267	DTIC/Paclitaxel (n= 108)	1.5 (1.4, 2.7)	HR 0.45 (0.33, 0.63) p<0.001	MEK114267 & Clinical Study Report[1]
		Trametinib (n= 214)	4.8 (4.3, 4.9)		
Vemurafenib	BRIM-3	DTIC (n=337)	1.6 (1.5, 1.7)	HR 0.26 (0.20, 0.33) p<0.0001	See footnote 3
		Vemurafenib (n=338)	5.3 (4.8; 6.6)		
Dabrafenib	BRF113683	DTIC (n=63)	2.7 (1.5, 3.2)	HR 0.3 (0.18, 0.51) p<0.0001	BRF11368 Clinical Study Report[2]
		Dabrafenib (n=187)	5.1 (4.9. 6.9)		

Notes:

1. MEK114267 CSR Table 16; Source Table 7.4 (m5.3.5.1)
2. BRF113683 CSR Table 15; Source Table 7.1015 (m5.4)
3. FDA.gov website, 2013

The overall response rate (ORR) for trametinib in the intent to treat population of MEK114267 (22%) was lower than that reported for BRF113683 (50%) or BRIM-3 (48%). However the proportion of patients with stable disease was higher for trametinib treated patients in the MEK114267 study (56%) compared to BRF113683 (42%). The median duration of response for patients receiving trametinib in MEK114267 was 5.5 months, which was similar to the duration of response observed in BRF113683 (5.6 months) and BRIM-3 (5.5 months).

Supportive study(ies)

Trametinib monotherapy

Study MEK113583

MEK113583 was an open-label, Phase II, multicentre study designed to evaluate the ORR following daily oral dosing of trametinib at a dose of 2.0 mg once daily. This study enrolled patients with BRAF V600E, V600K or V600D mutation-positive histologically or cytologically confirmed diagnosis of metastatic cutaneous melanoma. For this study patients were enrolled into two separate cohorts defined by prior therapy received: patients that had been previously treated with a BRAF inhibitor, and those who had not.

Efficacy endpoint included ORR, duration of response, PFS and OS. The ORR was calculated from investigator assessments of tumour disease progression and response as defined by RECIST v 1.1 (Eisenhauer, 2009). Assessments were performed at screening and every 8 weeks (± 5 days) on a calendar schedule and were not affected by dose interruptions/delays.

No confirmed CRs or PRs were observed in Cohort A, comprising patients who had received prior therapy with a BRAF inhibitor. The confirmed ORR in Cohort B, comprising patients who had not received prior therapy with a BRAF inhibitor, was 25%. The median PFS in this cohort was 4.0 months, and the 6-and 12 month OS rates were 79% and 50% respectively. The OS data were not mature. The median follow-up time at the data cut-off date (4 April 2013) was 13.8 months.

Study MEK111054

See section 2.5.1

Combination Trametinib-Dabrafenib

For the combination treatment the study BRF11322220 part C was considered the pivotal study, whereas BRF113220 Parts B and D and results of the sub population of BRAFi-treated patients were considered supportive results.

BRF113220 Part B

For Part B of the BRF113220 study patients were enrolled in escalating dose cohorts of dabrafenib and trametinib in a 3+3 design. The highest 3 cohorts (150/1, 150/1.5 and 150/2) were expanded to a maximum of 25 patients (actual range 22-26) to further characterize the safety profile of combination treatment. Upon completion of dose escalation, 2 additional efficacy expansion cohorts were opened, one cohort enrolling patients with BRAF V600-mutation positive melanoma who had experienced disease progression following prior treatment with a small-molecule BRAF inhibitor and the other cohort enrolling patients with BRAFV600 mutation-positive colorectal cancer. The 150/2 dabrafenib/ trametinib combination therapy cohort, 24 patients were enrolled. These patients were BRAFi-naïve.

For this cohort a median investigator-assessed PFS of 10.8 months (95% CI: 5.3, 14.4) was reported. The investigator-assessed confirmed ORR was 63% (95% CI: 40.6, 81.2), and the median duration of response was 11.3 months (95% CI: 9.1, 16.9).

BRF113220 Part D

Due to its improved long-term stability, a HPMC capsule shell was selected as the commercial formulation of dabrafenib, instead of the gelatin capsule shell used in the early clinical development program. Because the dose escalation in Part B was conducted using gelatin capsules, Part D was performed to assess the impact of this change in the dabrafenib capsules shell on PK and the safety profile of the combination. Patients were included into four different cohorts; 75 mg BID dabrafenib monotherapy, 150 mg BID dabrafenib monotherapy, 75 BID dabrafenib plus 2 mg QD trametinib combination therapy and 150 BID dabrafenib plus 2 mg QD trametinb combination therapy. Efficacy was evaluated in patients included in this part of the BRF113220 study as secondary endpoint.

For the 39 BRAFi-naïve patients treated with combination 150/2 therapy in part D of BRF113220, the Kaplan-Meier estimate for median PFS was not reached after median follow-up of 7.7 months. Investigator-assessed confirmed response rate was 67% (95% CI: 49.8, 80.9). At the time of analysis, follow-up was ongoing in 77% of the responding patients and the median duration of response was not reached.

BRAFi-treated patients

The patients population that was previously treated with BRAF–inhibitors consist of patients included in Part C of the BRF113220 study who have been randomized to the dabrafenib monotherapy arm and who crossed over to 150/2 combination therapy after progression. Furthermore, in Part B of the BRF113220 study 26 patients were included who had previously treated with a BRAF inhibitor.

For the 43 patients of the BRF113220 part C study, that crossed over from dabrafeinib monotherapy to 150/2 combination therapy a median PFS in the crossover phase was 3.6 months (95% CI: 1.8, 3.9) was reported. The best confirmed ORR in the crossover phase was 9% (95 CI: 2.6, 22.1), with 47% of the patients achieving SD and 37% having an assessment of progressive disease.

For the 26 patients of the BRF113220 part B study who had been previously treated with a BRAF inhibitor the median investigator-assessed PFS was 3.6 months (95% CI: 1.9, 5.2). The investigator-assessed confirmed response rate was 15% (95% CI: 4.4, 34.9), all responses were partial responses.

2.5.3. Discussion on clinical efficacy

Two indications were initially sought for Mekinist (trametinib):

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

Part C of trial Study BRF113220 was presented as pivotal to support this combination.

2- Trametinib monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Trametinib monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy.

Study MEK114267 was submitted as pivotal to support the MEK inhibitor trametinib monotherapy for systemic treatment in stage IIIc or IV melanoma. Although an open-label study, it was implemented under a Data Management Study Blinding Plan that outlined procedures for eliminating bias. OS analysis is considered a valuable secondary endpoint, also with respect to the influence of the open label status on the results on primary endpoint PFS. The open label design is understood since the treatment in the study arm varies intrinsically (oral versus iv use).

Study BRF113220 was to show that trametinib in combination with BRAF inhibitor dabrafenib leads to more prolonged PFS in comparison to BRAF inhibition monotherapy (dabrafenib). During the procedure, results of the phase III study MEK115306 were submitted to confirm the results obtained in the BRF113220 study.

The proposed dose of 2 mg QD was established based on better tolerability and similar efficacy of 2 mg when compared to higher dose groups also regarding the objective tumour response.

Design and conduct of clinical studies

The submitted pivotal studies, MEK114267 and BRF113220, address the issue of treatment of BRAF V600 mutation positive melanoma. In line with the defined signal transduction of the RAS-RAF and subsequently the MEK-Erk pathways the MEK inhibition with trametinib as well as the combination of trametinib with BRAF inhibitor dabrafenib is sought. The study MEK114267 was a phase III trial in which 322 patients were included. Study endpoints as well as the assessment of efficacy parameters were acceptable. The choice of the comparator treatment in the control-arm of this study MEK114267, dacarbazine or paclitaxel represented the options available for systemic palliative treatment of the disease at the time of conducting the trial as no other treatment options (e.g. ipilimumab, vemurafenib) for melanoma were licenced at that time.

In the clinical studies only patients with cutaneous melanoma were studied. Efficacy in patients with ocular or mucosal melanoma has not been assessed (SmPC section 5.1).

MEK114267 included 322 from 1059 screened. Although approximately 50% patients are expected to be ineligible because of BRAF-wild type status, exclusion of an additional 20% of patients was considered high. These exclusions were likely to be due to stringent criteria for brain metastases and strict inclusion/exclusion criteria.

BRF113220 Part C was a phase II trial that encompassed 162 patients. The study MEK115306 was a phase III study including 423 patients. The primary and secondary endpoints of this study, including PFS, OS and the RR) were considered appropriate.

Efficacy data and additional analyses

There was a statistically significant improvement of the primary endpoint PFS compared with the comparator arm(s) in both pivotal trials. Regarding study MEK114267, the other endpoints OS, ORR and DoR are considered supportive for the demonstration of better efficacy of trametinib monotherapy compared to chemotherapy. No imbalance in post-study treatment was observed.

In the MEK115306 study the difference in median PFS between trametinib in combination with dabrafenib and dabrafenib monotherapy was 0.5 month and in BRF113220 part C it was3.6 months. For MEK115306 study the HR for PFS as assessed by the investigator was 0.75 (95%CI: 0.57, 0.99), p=0.035 and assessed by a independent reviewer (IRC) was 0.78 (95% CI: 0.59, 1.04). For BRF113220 part C study the HR as assessed by the investigator was HR of 0.39 (95% CI: 0.25, 0.62; p<0.0001) and as assessed by the BIRC was 0.54 (95% CI: 0.32, 0.91; p=0.0121). In terms of OS, the data were too immature to draw any conclusions.

The OS analysis of the pivotal MEK114267 study is confounded by large crossover among the 108 patients treated with chemotherapy as 70 patients (65%) crossed over to trametinib treatment.

Trametinib monotherapy has not been compared with a BRAF inhibitor in a clinical study in patients with BRAF V600 mutation positive unresectable or metastatic melanoma. Based on cross-study comparisons, overall survival and progression free survival data appear to show similar effectiveness between trametinib and BRAF inhibitors; however, overall response rates were lower in patients treated with trametinib than those reported in patients treated with BRAF inhibitors (SmPC section 4.4).

Trametinib monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy (SmPC section 4.1)

Resistance to BRAF inhibition is a known phenomenon. This acquired resistance can be explained by the appearance of secondary mutations in NRAS or by mutations in MEK in a subpopulation of patients (Trunzer et al., Clin Oncol. 2013).

The most frequent mutation is BRAFV600E, which occurs in approximately 80-95% of the BRAF-mutated population, whereas the BRAFV600K mutation occurs in approximately 5-20% of the BRAF-mutated population. The clinical phenotype in BRAF V600K-mutant melanoma appears more aggressive, with a shorter time from first diagnosis to metastasis and death due to a higher prevalence of brain and lung metastases [El-Osta, 2011]. In clinical trials, central testing for BRAF V600 mutation using a BRAF mutation assay was conducted on the most recent tumour sample available. Primary tumour or tumour from a metastatic site was tested with a validated polymerase chain reaction (PCR) assay developed by Response Genetics Inc. The assay was specifically designed to differentiate between the V600E and V600K mutations.

Subsequently, all patient samples were re-tested using the CE marked bioMerieux (bMx) THxID BRAF validated assay. The bMx THxID BRAF assay is an allele-specific PCR performed on DNA extracted from FFPE tumour tissue. The assay was designed to detect the BRAF V600E and V600K mutations with high sensitivity (down to 5 % V600E and V600K sequence in a background of wild-type sequence using DNA extracted from FFPE tissue). Non-clinical and clinical studies with retrospective bi-directional Sanger sequencing analyses have shown that the test also detects the less common BRAF V600D mutation and V600E/K601E mutation with lower sensitivity. Of the specimens from the non-clinical and clinical studies (n = 876) that were mutation positive by the THxID BRAF assay and subsequently were sequenced using the reference method, the specificity of the assay was 94 % (SmPC section 5.1).

Whilst the ORR appeared to be lower in patients with tumours expressing the V600K mutation, efficacy in terms of PFS was similar comparing V600E and V600K. The CHMP concluded that there was enough evidence to support a broader indication of “V600 mutation” and not to restrict the indication to BRAF V600E patient population. Before taking trametinib patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test (SmPC section 5.1).

The appropriateness of the selected dose of trametinib 2 mg for patients with BRAF V600E mutation positive melanoma and the possibility of up-titration (e.g., with the V600K mutation) were discussed. AEs leading to dose interruptions/delay were observed in 32/70 (46%) of patients treated with 2 mg vs. 36/62 (58%) with 2.5 mg. More importantly 8/70 vs. 25/62, 2 and 2.5 mg, respectively had the dose reduced. Based on these data, up-titration of the dose cannot be recommended.

The safety and efficacy of trametinib have not been evaluated in patients whose melanoma tested negative for the BRAF V600 mutation.

An attempt was made to compare the efficacy of trametinib to that of other BRAF inhibitors. There is no clinical study directly comparing the efficacy of monotherapy trametinib with a BRAF-inhibitor, therefore, no definitive conclusion can be drawn. Based on indirect cross-study comparisons the effect on PFS and OS was comparable to what reported for BRAF inhibitors, however the ORR was notably lower. The molecular basis for this difference is not known. Objective tumour response is assumed to be beneficial in situations where tumour mass is associated with symptoms. The difference in ORR has been reflected in the SmPC (SmPC section 4.4).

The proportion of patients that received BRAF inhibition and Ipilimumab as post progression treatment was comparable for the two study groups. Also, no big differences were seen in time on post progression treatment (vemurafenib or ipilumumab; data not shown). The response on ipilimumab was not worse for patients who were earlier treated with trametinib than for patients treated with chemotherapy (24% versus 18%). The reported response rates for BRAF inhibition therapy after trametinib and after chemotherapy were comparable (CR+PR 17% versus 17; data not shown).

In view of the low response rate reported with trametinib as first line, and with a BRAF inhibitor as second line after progression on trametinib, there might be a patient group that doesn't respond on trametinib treatment and misses the opportunity to benefit from first line BRAF-inhibition.

According to the baseline characteristics of BRF113220 study, an imbalance in percentage of patients having received previous chemotherapy was observed. Prior chemotherapy could imply comparably worse prognosis of patients at the moment next line treatment is indicated. The 150/2 group can be considered favoured with a relatively larger group of chemotherapy-naïve patients.

Due to the limited number of patients enrolled in study BRF113220, the baseline imbalances in prior treatments potentially favouring the combination, in important factors and the immature OS data, results of the MEK115306 study, on the combination of trametinib and dabrafenib were submitted. The PFS results of MEK115306 were less favourable than those observed in the phase I/II trial BRF113220 (HR=0.75 instead of 0.39, difference in PFS 5-10% instead of 20%) and clinical relevance has not robustly been established. The efficacy results are considered borderline, at best, from a statistical perspective (p= 0.035, investigator and p=0.085, IRC). Furthermore, at an event rate of about 50% in the investigator analysis and apparent heterogeneity in activity in relation to prognostic factors (higher activity in patients with poor prognosis), differences might further reduce with longer follow-up. A clearly higher event rate is thus needed for data to be mature enough. The available OS data are still immature and no definitive conclusion can be drawn regarding benefit on OS of the combination therapy.

2.5.4. Conclusions on the clinical efficacy

The pivotal and supportive trials favour the monotherapy trametinib for patients with BRAF mutation positive melanoma compared with chemotherapy. Cross study comparison show that the benefit regarding PFS and OS of trametinib monotherapy is comparable to the results previously reported for BRAF inhibitors, however the ORR reported for trametinib seems to be lower for trametinib than for vemurafenib or dabrafenib. The efficacy results of trametinib monotherapy for the treatment of BRAF V600 mutated malignant melanoma can be considered demonstrated. More importantly, trametinib monotherapy could be considered an option in patients for whom BRAF inhibition is not a suitable alternative. Regarding the trametinib dabrafenib combination the efficacy has not been established.

2.6. Clinical safety

Trametinib monotherapy

Overall approximately 1749 patients with cancer have been exposed to at least one administration of trametinib at various doses, either as monotherapy or in combination with approved drugs or experimental compounds. A total of 1185 subjects received 2 mg of trametinib, of which 329 patients had melanoma and were treated with trametinib 2 mg monotherapy once daily.

The safety database of trametinib has been presented in 3 different populations:

- *Integrated trametinib monotherapy safety population (TISS):* 329 patients with melanoma treated with trametinib 2 mg once daily, of which 211 patients included in the phase III MEK114267-cross over study, 97 patients enrolled in the phase II MEK113583 study and 21 in the phase I MEK111054 study. Of note, data from the 68 patients enrolled in the MEK114267 study who had cross-over to trametinib at the time of the cut-off for the MEK114267 study were not included in the TISS.

- *Population enrolled in the phase III MEK114267 study*: 310 patients with metastatic melanoma, of which 211 patients treated with trametinib 2 mg once daily 99 patients treated with chemotherapy (paclitaxel or dacarbazine at discretion of the investigator).

- *OCEANS:* SAEs from patients enrolled in the trametinib clinical program are provided from the GSK Global safety database, referred to as OCEANS.

Combination Trametinib-Dabrafenib

For the combination treatment Trametinib-Dabrafenib, safety data from study BRF113220 are presented in comparison with updated safety data from the TISS for trametinib (uTISS, data cut-off date 23 June 2012) and dabrafenib (DISS, data cut-off date 25 June 2012). Safety data from 6 groups of patients with unresectable or metastatic BRAFV600-mutation positive melanoma are evaluated as follows:

- *Part C 150/2 population (primary safety population):* the 55 patients treated with dabrafenib 150 mg BID and trametinib 2 mg QD in Part C of Study BRF113220.

- *Pooled 150/2 population:* the 202 patients treated with dabrafenib 150 mg BID and trametinib 2 mg QD in Parts B, C, and D of Study BRF113220, including patients who initially received monotherapy and crossed over to receive 150/2 combination therapy (only safety data collected during combination treatment are included).

- *Trametinib Integrated Summary of Safety population (uTISS):* updated safety data (cut-off date 23 June 2012) from the 329 subjects in the TISS, who received trametinib 2 mg QD as monotherapy.

- *Dabrafenib Integrated Summary of Safety population (DISS):* updated safety data (cut-off date 25 June 2012) from the 586 patients who received dabrafenib 150 mg BID as monotherapy, originally included in the original submission for MAA (ongoing procedure).

- *Part C Dabrafenib Monotherapy treatment group:* the 53 patients treated with dabrafenib 150 mg BID as monotherapy in Part C of Study BRF113220.

- *Pooled Any Combination Dose population (PACDP):* includes all 365 patients who received at least one dose of the combination regimen irrespective of the specific dabrafenib or trametinib dose in parts B, C, and D of Study BRF113220. Part A was not included because patients were not allowed to receive combination treatment until the combination dose was determined in Part B.

Furthermore, a comparison of the safety of HPMC and gelatin based dabrafenib combination regimens is provided.

During the procedure, the Applicant provided a safety update regarding the above mentioned safety populations. Essentially, the updated data are in line with the data presented during the original submission.

Moreover, according to the Applicant Phase III studies MEK115306 and MEK116513, further investigating the combination of dabrafenib and trametinib, are currently ongoing.

Table 33: Safety Populations

Population	Number of Subjects	Dose	Designation in this ISS
Study BRF113220 Part C combination therapy	55	dabrafenib 150 mg BID + trametinib 2 mg QD	Part C 150/2 group
Study BRF113220 Parts B/C/D combination therapy	202	dabrafenib 150 mg BID + trametinib 2 mg QD	Pooled 150/2 population
Trametinib ISS Safety Update	329	trametinib 2 mg QD	Trametinib ISS population
Dabrafenib ISS Safety Update	586	dabrafenib 150 mg BID	Dabrafenib ISS population
Study BRF113220 Part C dabrafenib monotherapy	53	dabrafenib 150 mg BID	Part C Dabrafenib Monotherapy group
Study BRF113220 Parts B/C/D combination therapy	365	any combination dose	Pooled Any Combination Dose population

BID = two times a day; QD = once daily.

Patient exposure

Trametinib monotherapy

At the data cut-off date, 107 patients (33%) in the TISS were treated with trametinib for more than 6 months. Median duration of treatment was longer in the trametinib arm of the pivotal MEK114267 study (4.83 months) and the TISS (3.84 months) compared with the chemotherapy arm (2.07 months). The mean daily dose was 1.85 mg (93% of the targeted 2 mg dose) in the TISS and 1.81 mg (or 91%) in the trametinib arm of the MEK114267 study.

In the MEK114267 study and in the TISS a similar frequency of dose reductions (32% and 29%, respectively) and dose delay/interruptions (41% and 44%, respectively) were reported, and the frequency was significantly higher than frequencies observed in the chemotherapy arm of the pivotal MEK114267 study (11% and 27%, respectively). The most frequent reasons for dose modifications were AEs (>80%). In the trametinib arm of the MEK114267 study and in the TISS 7-9% of patients required 2 dose reductions or delay/interruptions, versus 1-5% of patients treated with chemotherapy in the pivotal study. Dose re-escalations were implemented in 11 patients (4%) in the TISS.

Combination Trametinib-Dabrafenib

At the time of the data cut-off for Part C of Study BRF113220 (31 May 2012), most patients in the Part C 150/2 treatment group (74%) were still ongoing in the study (on treatment, in the cross-over phase or in follow-up). The proportion of patients still on treatment was higher in the Part C 150/2 group (43%) compared with the Part C dabrafenib monotherapy group (30%), the Pooled 150/2 population (36%) and the PACDP (39%). Discontinuation due to AEs was more common in the Part C 150/2 group (13%) compared with the Part C Dabrafenib Monotherapy group (2%). Similar low percentages of discontinuation due to AEs were reported in the pooled 150/2 population and in the PACDP (7%). As of the data cut-off, 93% and 73% of patients had discontinued study treatment in the uTISS and DISS, respectively, with disease progression being the most frequent reason for discontinuation.

Median daily dose of dabrafenib was 281.75 mg in the Part C 150/2 group, 295.91 mg in the Part C Dabrafenib monotherapy group, and 285.58 mg in the Pooled 150/2 population. The median daily dose of trametinib was 1.92 mg in the Part C 150/2 group, and 1.95 mg in the Pooled 150/2 population.

The median time on study treatment was longer in Part C 150/2 group (10.9 months for both dabrafenib and trametinib) compared with the uTISS (3.84 months), and the DISS (5.47 months). Of note, the median time of therapy in the Part C 150/2 group was also longer than the Pooled 150/2 Population (6.5 months), essentially due to shorter follow up achieved by several subgroups included in the pooled population (Part C crossover, Part D, BRAF-I pre-treated patients) at the time of the analysis.

Additional safety data for the combination treatment were obtained by the phase III MEK115306 study. The safety population of MEK115306 included 420 patients; 209 patients were treated with dabrafenib and trametinib in combination and 211 patients were treated with dabrafenib monotherapy.

Adverse events

Trametinib monotherapy

Adverse events (AEs) were coded using MedDRA v14.1 in MEK111054 and v15.0 in the MEK113583 and MEK114267 studies, and graded using the National Cancer Institute Common Toxicity Criteria (version 3.0 [MEK111054 and MEK113583] and version 4.0 [MEK114267]).

Table 34: Adverse Events Overview in MEK114267 study and the TISS

	MEK114267		Integrated Safety Population
	Chemotherapy (N=99)	Trametinib (N=211)	Trametinib (N=329)
Any AE, n (%)	**92 (93)**	**209 (>99)**	**326 (>99)**
AEs drug-related	79 (80)	205 (97)	314 (95)
AEs leading to permanent discontinuation of study drug*	9 (9)	26 (12)	32 (10)
AEs leading to dose reduction	10 (10)	68 (32)	85 (26)
AEs leading to dose delay/interruption	24 (24)	80 (38)	117 (36)
Any SAE, n (%)	**20 (20)**	**50 (24)**	**74 (22)**
SAEs drug-related	11 (11)	26 (12)	33 (10)
Fatal SAEs	2 (2)	4 (2)	5 (2)
Fatal SAEs drug-related	0	1 (<1)	1 (<1)

The most common AEs in subjects treated with trametinib in the integrated studies included rash, diarrhea, fatigue, edema peripheral, nausea, dermatitis acneiform and vomitting. Among the common AEs in MEK114267, rash, diarrhea, edema peripheral, dermatitis acneiform, dry skin, pruritis, paronychia and hypertension were more frequent in the trametinib arm, while nausea, vomiting and constipation were more frequent in the chemotherapy arm.

Most AEs in the TISS and trametinib arm of the MEK114267 study were Grade 1 or 2. The most common Grade 3 AEs were hypertension and rash. Five subjects in the TISS had Grade 5 AEs (1 gastrointestinal fistula, 1 hepatic and renal failure; 1 myocardial infarction; 1 renal failure; 1 death due to unknown causes).

The majority of AEs in the chemotherapy arm of the pivotal MEK114267 study were Grades 1 and 2. The most common Grade 3 AEs were fatigue and hypertension; two fatal SAEs were reported (pneumonia, pseudomembranous colitis).

Table 35: Adverse Events Reported by ≥ 10% of All Subjects by Preferred Term and Maximum Toxicity Grade plus AEs Reported by >1% of Subjects with Grade 3 or Grade 4 Events in Either Treatment Arm of MEK114267 or in the Integrated Trametinib Safety Population

	MEK114267						Integrated Safety Population		
	Chemotherapy (N=99) n (%)			Trametinib (N=211) n (%)			Trametinib (N=329) n (%)		
	Maximum Grade								
	Any Grades	3	4	Any Grades	3	4	Any Grades	3	4
Any event	**92 (93)**	**27 (27)**	**5 (5)**	**209 (>99)**	**97 (46)**	**12 (6)**	**326 (>99)**	**138 (42)**	**23 (7)**
Preferred Term									
Rash	10 (10)	0	0	124 (59)	17 (8)	1 (<1)	191 (58)	24 (7)	1 (<1)
Diarrhoea	17 (17)	1 (1)	1 (1)	93 (44)	1 (<1)	0	162 (49)	5 (2)	0
Fatigue	28 (28)	3 (3)	0	61 (29)	9 (4)	0	109 (33)	15 (5)	0
Oedema peripheral	3 (3)	0	0	62 (29)	3 (1)	0	109 (33)	6 (2)	0
Nausea	39 (39)	1 (1)	0	46 (22)	2 (<1)	0	99 (30)	3 (<1)	0
Dermatitis acneiform	2 (2)	0	0	41 (19)	2 (<1)	0	74 (22)	6 (2)	0
Vomiting	20 (20)	2 (2)	0	31 (15)	3 (1)	0	66 (20)	5 (2)	0
Constipation	23 (23)	1 (1)	0	33 (16)	1 (<1)	0	61 (19)	1 (<1)	0
Dry skin	1 (1)	0	0	27 (13)	0	0	57 (17)	0	0
Alopecia	19 (19)	0	0	38 (18)	2 (<1)	0	51 (16)	2 (<1)	0
Pruritus	1 (1)	0	0	24 (11)	4 (2)	0	54 (16)	5 (2)	0
Hypertension	7 (7)	3 (3)	0	35 (17)	28 (13)	0	48 (15)	29 (9)	0
Abdominal pain	2 (2)	1 (1)	0	17 (8)	2 (<1)	0	43 (13)	5 (2)	1 (<1)
Decreased appetite	10 (10)	0	0	17 (8)	1 (<1)	1 (<1)	42 (13)	3 (<1)	1 (<1)
Headache	15 (15)	0	0	29 (14)	3 (1)	0	38 (12)	3 (<1)	0
Pyrexia	11 (11)	1 (1)	0	14 (7)	1 (<1)	0	40 (12)	2 (<1)	0
Cough	6 (6)	0	0	23 (11)	0	0	37 (11)	0	0
Dyspnoea	6 (6)	0	0	15 (7)	3 (1)	1 (<1)	35 (11)	4 (1)	1 (<1)
Arthralgia	9 (9)	0	0	20 (9)	2 (<1)	0	33 (10)	4 (1)	0
AST increased	1 (1)	0	0	21 (10)	3 (1)	1 (<1)	32 (10)	5 (2)	1 (<1)
Dry mouth	2 (2)	0	0	18 (9)	0	0	34 (10)	0	0
Anaemia	11 (11)	0	0	13 (6)	4 (2)	0	31 (9)	9 (3)	2 (<1)
Insomnia	7 (7)	0	0	15 (7)	0	0	28 (9)	0	0
ALT increased	3 (3)	0	0	18 (9)	7 (3)	0	25 (8)	9 (3)	0
Hypoalbuminaemia	1 (1)	1 (1)	0	8 (4)	3 (1)	0	20 (6)	5 (2)	0
Cellulitis	0	0	0	4 (2)	3 (1)	0	17 (5)	8 (2)	0
Pain in extremity	8 (8)	2 (2)	0	11 (5)	1 (<1)	0	23 (7)	1 (<1)	0
Blood creatine phosphokinase increased	0	0	0	8 (4)	4 (2)	0	8 (2)	4 (1)	0
Dehydration	1 (1)	0	1 (1)	4 (2)	3 (1)	1 (<1)	14 (4)	6 (2)	1 (<1)
Pulmonary embolism	1 (1)	0	0	6 (3)	4 (2)	1 (<1)	12 (4)	7 (2)	4 (1)
Chest pain	4 (4)	0	0	7 (3)	0	0	7 (2)	0	0
Hyponatraemia	1 (1)	1 (1)	0	3 (1)	2 (<1)	1 (<1)	11 (3)	6 (2)	1 (<1)
Syncope	0	0	0	5 (2)	2 (<1)	0	8 (2)	5 (2)	0
Peripheral sensory neuropathy	9 (9)	3 (3)	0	3 (1)	0	0	4 (1)	0	0

Almost all subjects (95%) treated with trametinib in the TISS had AEs considered as drug-related by the investigator (see Table).

Table 36: Summary of Common Drug-Related Adverse Events Reported by ≥10% of Subjects in Either Treatment Arm of MEK114267 or the Integrated Trametinib Safety Population

Preferred term	MEK114267		Integrated Safety Population
	Chemotherapy (N=99) n (%)	Trametinib (N=211) n (%)	Trametinib (N=329) n (%)
Any drug-related event	**79 (80)**	**205 (97)**	**314 (95)**
Rash	3 (3)	121 (57)	187 (57)
Diarrhoea	12 (12)	70 (33)	128 (39)
Fatigue	21 (21)	41 (19)	74 (22)
Dermatitis acneiform	0	40 (19)	73 (22)
Oedema peripheral	0	36 (17)	71 (22)
Nausea	31 (31)	30 (14)	63 (19)
Dry skin	1 (1)	25 (12)	51 (16)
Pruritus	0	23 (11)	51 (16)
Alopecia	19 (19)	34 (16)	45 (14)
Vomiting	16 (16)	13 (6)	33 (10)

Table 35: summarises the adverse events for which it was considered that there is sufficient evidence to suggest a causal relationship with the administration of trametinib.

Table 37: Adverse reactions occurring in patients treated with trametinib in the integrated safety population (n=329)

System Organ Class	Adverse Reactions	Frequency (%)
Blood and lymphatic system disorders	Anaemia	9%
Immune system disorders	Hypersensitivity[a]	1%
Metabolism and nutrition disorders	Dehydration	4%
Eye disorders	Vision blurred	6%
	Periorbital oedema	3%
	Visual impairment	2%
	Chorioretinopathy	<1%
	Papilloedema	<1%
	Retinal detachment	<1%
	Retinal vein occlusion	<1%
Cardiac disorders	Left ventricular dysfunction	4%
	Ejection fraction decreased	5%
	Cardiac failure	<1%
Vascular disorders	Hypertension	15%
	Haemorrhage[b]	16%
	Lymphoedema	7%
Respiratory, thoracic and mediastinal disorders	Cough	11%
	Dyspnoea	11%
	Pneumonitis	2%
	Interstitial lung disease	<1%
Gastrointestinal disorders	Diarrhoea	49%

System Organ Class	Adverse Reactions	Frequency (%)
	Nausea	30%
	Vomiting	20%
	Constipation	19%
	Abdominal pain	13%
	Dry mouth	10%
	Stomatitis	7%
Skin and subcutaneous disorders	Rash	58%
	Dermatitis acneiform	22%
	Dry skin	17%
	Pruritus	16%
	Alopecia	16%
	Erythema	5%
	Palmar-plantar erythrodysaesthesia syndrome	4%
	Skin fissures	3%
	Skin chapped	5%
Musculoskeletal and connective tissue disorders	Rhabdomyolysis	<1%
General disorders and administration site conditions	Fatigue	33%
	Oedema peripheral	33%
	Pyrexia	12%
	Face oedema	7%
	Mucosal inflammation	7%
	Asthenia	5%
Infections and infestation	Folliculitis	9%
	Paronychia	8%
	Cellulitis	5%
	Rash pustular	3%
Investigations	Aspartate aminotransferase increased	10%
	Alanine aminotransferase increased	8%
	Blood alkaline phosphatase increased	5%
	Blood creatine phosphokinase increased	2%

[a] May present with symptoms such as fever, rash, increased liver function tests, and visual disturbances
[b]Events include: epistaxis 8%, haematochezia 2%, gingival bleeding 1%, haematuria <1%, and rectal 1%, haemorrhoidal <1%, gastric <1%, vaginal 2%, conjunctival <1%, and post procedural haemorrhage <1%.

Combination Trametinib-Dabrafenib

The overall AE profile was similar between the Part C 150/2 and the Pooled 150/2 population, and between the DISS and the Part C Dabrafenib monotherapy arm.

Table 38: Overview of Adverse Events (All Treated or Safety Population)

	Combination Therapy		Monotherapy		
	Dabrafenib + Trametinib		Trametinib	Dabrafenib	
	BRF113220 Part C	BRF113220 Pooled	ISS	ISS	BRF113220 Part C
Dabrafenib	150 mg BID	150 mg BID	--	150 mg BID	150 mg BID
Trametinib	2 mg QD	2 mg QD	2 mg QD	--	--
N	55	202	329	586	53
Any AE, n (%)	**55 (100)**	**201 (>99)**	**326 (>99)**	**566 (97)**	**53 (100)**
Drug-related AEs	55 (100)	184 (91)	314 (95)	517 (88)	51 (96)
AEs leading to permanent discontinuation of study drug	5 (9)	17 (8)	32 (10)	17 (3)	1 (2)
AEs leading to dose reduction	27 (49)	97 (48)	85 (26)	100 (17)	11 (21)
AEs leading to dose interruption	37 (67)	126 (62)	117 (36)	192 (33)	18 (34)
Any SAE, n (%)	**34 (62)**	**109 (54)**	**74 (22)**	**174 (30)**	**13 (25)**
SAEs leading to hospitalization (protocol defined)[a]	21 (38)	70 (35)	NA	NA	12 (23)
Drug-related SAEs	23 (42)	78 (39)	33 (10)	114 (19)	10 (19)
Fatal SAEs	3 (5)	7 (3)	5 (2)	8 (1)	0
Drug-related fatal SAEs	0	1 (<1)	1 (<1)	1 (<1)	0

Data Source: m5.3.5.3 ISS Section 2.1

BID = two times a day; NA=not available; QD = once daily

a. In addition to the standard definition of SAEs, the BRF113220 protocol mandated that the following events were to be reported as SAEs, regardless of whether the subjects were hospitalized: SCC; LVEF decreases meeting protocol-defined stopping criteria; CSR or RVO, valvular toxicity meeting protocol-defined stopping criteria; new primary cancers; and pyrexia accompanied by hypotension and/or rigors/chills. Therefore, the total incidence of SAEs is higher than the incidence of SAEs that led to hospitalization.

Table 39: Adverse Events Experienced by ≥10% of Subjects in Part C 150/2 Group (All Treated or Safety Population)

	Combination Therapy		Monotherapy		
	Dabrafenib + Trametinib		Trametinib	Dabrafenib	
	BRF113220 Part C	BRF113220 Pooled	ISS	ISS	BRF113220 Part C
Dabrafenib	150 mg BID	150 mg BID	--	150 mg BID	150 mg BID
Trametinib	2 mg QD	2 mg QD	2 mg QD	--	--
N	55	202	329	586	53
Any AE, n (%)	55 (100)	201 (>99)	326 (>99)	566 (97)	53 (100)
Pyrexia	39 (71)	116 (57)	40 (12)	176 (30)	14 (26)
Chills	32 (58)	87 (43)	18 (5)	77 (13)	9 (17)
Fatigue	29 (53)	77 (38)	109 (33)	151 (26)	21 (40)
Nausea	24 (44)	81 (40)	99 (30)	149 (25)	11 (21)
Vomiting	22 (40)	73 (36)	66 (20)	107 (18)	8 (15)
Diarrhea	20 (36)	54 (27)	162 (49)	91 (16)	15 (28)
Cough	16 (29)	47 (23)	37 (11)	78 (13)	11 (21)
Headache	16 (29)	55 (27)	38 (12)	177 (30)	15 (28)
Edema peripheral	16 (29)	40 (20)	109 (33)	54 (9)	9 (17)
Arthralgia	15 (27)	56 (28)	33 (10)	172 (29)	18 (34)
Rash	15 (27)	55 (27)	191 (58)	115 (20)	19 (36)
Night sweats	13 (24)	39 (19)	3 (<1)	22 (4)	3 (6)
Constipation	12 (22)	38 (19)	61 (19)	61 (10)	6 (11)
Decreased appetite	12 (22)	38 (19)	42 (13)	82 (14)	10 (19)
Myalgia	12 (22)	26 (13)	8 (2)	86 (15)	12 (23)
Back pain	10 (18)	22 (11)	23 (7)	65 (11)	6 (11)
Dry skin	10 (18)	23 (11)	57 (17)	52 (9)	3 (6)
Insomnia	10 (18)	15 (7)	28 (9)	37 (6)	4 (8)
Abdominal pain upper	9 (16)	13 (6)	20 (6)	33 (6)	4 (8)
Dermatitis acneiform	9 (16)	26 (13)	74 (22)	17 (3)	2 (4)
Dizziness	9 (16)	29 (14)	25 (8)	37 (6)	5 (9)
Muscle spasms	9 (16)	22 (11)	18 (5)	15 (3)	2 (4)
Pain in extremity	9 (16)	25 (12)	23 (7)	92 (16)	10 (19)
Abdominal pain	8 (15)	18 (9)	43 (13)	42 (7)	7 (13)
Actinic keratosis	8 (15)	19 (9)	3 (<1)	52 (9)	5 (9)
Erythema	8 (15)	15 (7)	18 (5)	38 (6)	1 (2)
Neutropenia	8 (15)	18 (9)	6 (2)	16 (3)	1 (2)
Anemia	7 (13)	34 (17)	31 (9)	52 (9)	3 (6)
Oropharyngeal pain	7 (13)	22 (11)	12 (4)	20 (3)	0
Urinary tract infection	7 (13)	26 (13)	15 (5)	16 (3)	5 (9)
Dehydration	6 (11)	21 (10)	14 (4)	17 (3)	1 (2)
Dry mouth	6 (11)	20 (10)	34 (10)	9 (2)	3 (6)
Pruritus	6 (11)	15 (7)	54 (16)	41 (7)	7 (13)
Rash generalized	6 (11)	12 (6)	1 (<1)	7 (1)	4 (8)

Data Source: m5.3.5.3 ISS Section 2.1.1
Abbreviations: BID = two times a day; QD = once daily

In the Part C 150/2 population, pyrexia, neutropenia and back pain were the most common Grade 3 AEs (5% each), and neutropenia (5%) was the most common Grade 4 AE, all observed at higher incidence compared with uTISS and DISS. However, grade 3 hypertension (2%) and grade 3 rash (0%) occurred at lower frequency compared to the uTISS (9% and 7%, respectively), as well as grade 3 SCC (4%) and hypophosphatemia (0%) compared with the DISS (7% and 4%, respectively).

Headline safety results show that the adverse event profile observed for the trametinib/dabrafenib combination in MEK115306 is consistent with that reported in BRF113220. With a few minor exceptions, overall AE, grade 3-4 SAE and fatal SAE rates in the MEK115306 were numerically lower than, or similar to, the rates reported in BRF113220 part C or previously pooled safety data from the combination treatment.

Pyrexia remains the most common adverse event in patients receiving trametinib plus dabrafenib combination therapy. Other common AEs in patients receiving combination therapy included fatigue, nausea, headache, and chills. No disturbing different frequencies of adverse events or the observation of unknown adverse events were reported in the MEK115306, as were already known for the combination treatment.

Adverse events of special interest (AESI)

Consistent with the expected pharmacology, preclinical toxicology profile and the mechanism of action of trametinib (MEK inhibition), dabrafenib (BRAF inhibition) and the population treated, AEs of special interest (AESI) related to trametinib are rash and other skin-related toxicities, diarrhoea, ocular events, cardiac-related events and QT prolongation, hypertension, hepatic events, pneumonitis, and oedema. AESI related to dabrafenib are pyrexia, cutaneous SCC (cuSCC), other treatment emergent malignancies including new malignant melanoma, uveitis, PPES, renal failure and pancreatitis.

In general the incidence of AESI in the trametinib arm of study MEK114267 was similar to the TISS and higher when compared to the chemotherapy arm. Of relevance, MEK-related skin-related toxicities, diarrhoea and hypertension appeared to be lower with the combination treatment (Part C 150/2 group of BRF 113220 study) compared with trametinib monotherapy (TISS), whereas the rate of ocular events was higher.

BRAF-related events of pyrexia and renal failure appeared to be higher with the combination treatment (Part C 150/2 group) compared with dabrafenib monotherapy (DISS), whereas the incidence of cuSCC and PPE events was lower. The observed reduction of several AEs (including rash and diarrhoea) in patients treated with the combination trametinib-dabrafenib compared with what it would have been expected when the drug is given as dabrafenib or trametinib monotherapy has been theoretically explained by inhibition (achieved by combination treatments) of paradoxical activation of RAF or MEK –MAP kinase pathways induced by single selective inhibition of BRAF or MEK.

Specific guidelines have been developed by the Applicant and implemented in the studies performed for prevention, early diagnosis and appropriate treatment of AESI.

Skin-related events were observed in 88% of patients treated with trametinib monotherapy compared with 14% of patients treated with chemotherapy in the MEK114267 study, 65% of patients treated with the combination trametinib-dabrafenib in Part C of the BRF113220 study and 45% of patients treated with dabrafenib monotherapy. They essentially consisted of rash (58% [grade 3/4: 7%/<1%] in TISS vs 27% [grade 3/4:0/0] in Part C 150/2) and dermatitis acneiform (22% [grade 3/4:2%/0%] in TISS vs 16%[grade 3/4:0/0] in Part C 150/2). They generally occurred within the first months of treatment; most cases were grade 1 or 2 severity and did not require any dose interruptions or dose reductions. Palmar-plantar erythrodysaesthesia (PPE) was observed in 4% (grade 3/4:0/0) of patients treated with trametinib monotherapy, versus no patients treated with chemotherapy, 7% (grade 3/4:0/0) of patients treated with the combination trametinib-dabrafenib and 17% (grade 3/4:0/0) of patients treated with dabrafenib monotherapy. The incidence of cutaneous SCC and keratoacanthoma (typical AEs related to BRAF inhibition) appears to be reduced in the combination therapy population (Part C 150/2: 7%) compared with the dabrafenib monotherapy population (DISS: 11%; Part C Dabrafenib monotherapy: 19%) whereas no cases were observed in patients treated with trametinib monotherapy. Median time to onset appears to be delayed in the combination group (152 days) compared with the dabrafenib monotherapy population (DISS: 63 days). No new primary melanoma were reported with the dabrafenib-trametinib combination therapy and in 1% of patients treated with the dabrafenib monotherapy population. Other new primary malignancies were sporadically seen in patients treated with dabrafenib ± trametinib (≤1%), but no specific pattern of development of new malignancies could be identified. Theoretically, reactivation of a previous cancer could be hypothesized, especially when harbouring a mutated RAS oncogene.

Pyrexia and pyrexia-related events (including influenza like symptoms, cytokine release syndrome and systemic inflammatory response syndrome) were the most frequently reported AEs observed with the combination therapy (71 % [39/55] of patients in BRF133220 and 51 % [107/209] of patients in MEK115306). The incidence and severity in the combination therapy was higher than with dabrafenib (DISS: 33%, grade 3/4: 2%/<1%) and trametinib (uTISS: 15%, grade 3/4:<1%/0) monotherapy. This is reflected also in the higher use of antipyretics (40%), NSAIDs (40%) and corticosteroids (25%, recommended as prophylaxis for recurrent [≥1] episodes) in patients receiving combination treatment compared to dabrafenib or trametinib monotherapy. The median time to onset was 30 days (2-330) with potential relation with dabrafenib dose and median duration of 7.5 days (1-435). Approximately 33% of patients treated with combination therapy experienced ≥3 occurrences of pyrexia with higher incidence of hospitalization (11%) compared with dabrafenib monotherapy, essentially due to associated hypotension (~10%), hyponatraemia (~10%) and renal failure (3%), usually responsive to fluid and salt repletion. Approximately 50% of patients required dose reductions and interruptions (57%), compared with 15% and 30%, respectively in the DISS, whereas pyrexia led to treatment withdrawn in 5% of cases (compared with none in the DISS).

Ocular events were observed in 13% of patients treated with trametinib monotherapy (essentially blurred vision [6%] and dry eye [3%]) and led to dose interruptions and reductions in 12% and 7% of cases, respectively. The majority of ocular AEs were grade 1/2, with grade 3/4 events observed only in ≤1% of patients. Retinal vein occlusion (RVO), potentially due to prolonged inhibition of the MAP-kinase signal transduction pathway leading to impairment of the blood retinal barrier and activation of the coagulation cascade, was observed in <1% of patients treated with trametinib as monotherapy or in combination with dabrafenib, whereas no cases were observed in patients treated with dabrafenib monotherapy. In all cases the RVO occurred in only one eye, after prolonged (at least 12 weeks) treatment, and in presence of predisposing factors (e.g., glaucoma, hypertension, elevated hematocrit, chronic non-ischemic vein occlusion) in the majority of cases. RVO events resulted in discontinuation of study treatment in all patients. There is a comparative low incidence of RVO as AE in reaction to the use of trametinib, the comparatively high rate of risk factors for RVO in the general population (hypertension, diabetes mellitus, hyperlipidaemia, OAC, glaucoma, and/or anti-phospholipid syndrome) in relation to the severity of the disease (metastasized melanoma) to be treated. Local treatment with intravitreal injections of anti-VEGF antibodies was given in few patients with improvement of visual acuity. RPED was observed in <1% of patients treated with trametinib as monotherapy or in combination with dabrafenib, versus no cases observed in patients treated with dabrafenib monotherapy. All AEs were bilateral, self-limiting, did not require therapy or even not required stopping treatment in case of grade 1 events, did not result in any long-term visual impairment and re-treatment with trametinib was successful in the majority of cases. In the most cases CSR occurred within the first or second week of treatment, with no clear dose- or exposure- relationship, and resolved within 2 weeks from diagnosis. Of note, trametinib-induced CSR appears to be different when compared with literature-reported data as all cases were bilateral, without gender differences and appear to resolve much faster. Papilledema and optic nerve edema were reported in ≤1% of patients treated with trametinib monotherapy or in combination with dabrafenib. The event was not always associated with presence of brain metastases or increased intracranial pressure and in one case improving was reported after trametinib discontinuation. Uveitis events (including iritis) were reported in 1% of patients treated with dabrafenib monotherapy and in 2% of patients treated with the combination trametinib-dabrafenib, whereas no cases were observed in patients treated with trametinib monotherapy. The median time to onset was 9 weeks and median time to resolution was 19 days with topical anti-inflammatory (corticosteroids) ophthalmic therapy.

None of the events was serious and permanent discontinuation of treatment was not required in any patient. Of note, uveitis events in patients treated with the combination dabrafenib-trametinib were frequently associated or anticipated by episodes of fever, and were characterized by longer median time to resolution and increased severity (grade 3 and 4 events were reported) compared with the events observed with dabrafenib monotherapy.

Diarrhoea was more frequently reported with trametinib monotherapy (49%) compared with the combination dabrafenib-trametinib (36%) and dabrafenib monotherapy (16%), with occurrence within the first 14 days of treatment. In all populations treated, most cases (98%) were grade 1 or 2 severity, with only 2% grade 3 and no grade 4 nor SAEs. Dose adjustments were required in 4% of patients, whereas no treatment discontinuation was reported.

Cardiac related events, including reduction of ejection fraction and left ventricular dysfunction, were observed in 9% of patients treated with trametinib monotherapy or with the combination trametinib-dabrafenib, compared with 2% of patients treated with dabrafenib monotherapy. Therefore, addition of dabrafenib to trametinib did not appear to worsen the cardiac-related AEs in terms of incidence and severity. Most of events remain asymptomatic, essentially due to early detection and treatment interruption. The majority of cases observed in patients treated with trametinib monotherapy were grade 1 or 2 events (76-76%); grade 3 events were reported in 2% of all patients treated (25-26% of the cardiac events) and no grade 4 events were observed. Median time of onset ranged between 58 and 84 days. Dose interruption due to cardiac-related events occurred in 58-75% of trametinib monotherapy treated patients, whereas dose reductions and treatment withdrawal were reported in 35-55% and <2 % of cases, respectively. About 10% of patients treated with trametinib monotherapy reported clinically meaningful reductions in LVEF (≥10% decrease in LVEF from baseline and below lower limit of normal [LLN]) leading to treatment interruption. Time to the nadir ranged from 28 to 526 days. In the majority of patients re-challenge was performed and was successful, whereas 16% of patients were withdrawn from study due to cardiac-related events.

Peripheral oedema was reported in around 40% of patients treated with trametinib monotherapy compared with 5% of patients treated with chemotherapy. Median time to onset was 43 days and median duration of the event was 42 days. In about 50% of cases oedema was associated with left ventricular dysfunction. Oedema AEs led to dose interruption in 6% of patients, to dose reduction in 1-2% of patients, and to treatment discontinuation in 2% of patients.

Hypertension was reported in 9% of patients treated with the combination dabrafenib-trametinib in the Part C 150/2 group, compared with 15% in the trametinib monotherapy population and 2% in the dabrafenib monotherapy population. Most of cases were Grade 1 or 2, 2% were Grade 3 and no Grade 4 or 5 were observed. There were no SAEs or discontinuations of study drug due to hypertension in any of the patients treated with the combination trametinib-dabrafenib. In patients treated with trametinib monotherapy dose reductions or interruptions due to hypertension were reported in ≤1% of cases.

Hepatic events were reported in around 12% of patients treated with trametinib monotherapy. Increased ALT (9%) and AST (10%) were the most frequently reported hepatic AEs, mostly of Grade 1 or 2 (72%), with median time to onset of 29 days and median duration of 33 days. No Hy's Law cases were identified. Dose modification or treatment withdrawal was reported in 2-4% of cases. The incidence of hepatic events was similar between patients treated with trametinib monotherapy and the combination trametinib-dabrafenib.

Renal failure was reported in 7% (4 patients) of patients treated with dabrafenib in combination with trametinib in the Part C 150/2 of study BRF113220, compared with <1% with dabrafenib monotherapy (DISS) and 2% with trametinib monotherapy (TISS). All events were Grade 3 severity, 50% of cases were considered SAEs and drug-related. Renal failure AEs were associated with pyrexia or diarrhoea in the majority of cases, where dehydration could be a contributing factor.

Pneumonitis and interstitial lung disease (ILD): In study MEK114267, 2 % (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 MEK115306, < 1 % (1/209) of patients treated with trametinib in combination with dabrafenib developed pneumonitis requiring hospitalisation. ILD was reported in <1% of patients treated with trametinib monotherapy, compared with no case in patients treated with the combination dabrafenib-trametinib or dabrafenib monotherapy. All events were serious and considered by the investigator to be possibly drug-related. In all cases, the event was reported as improving or resolved upon interruption of trametinib treatment and initiation of symptomatic therapy.

The incidence of **pancreatitis** was <1% in the patients treated with dabrafenib or trametinib monotherapy, and 1% in patients treated with the dabrafenib-trametinib combination. Discontinuation of study drug was not considered necessary in any case.

The incidences of **QTc** ≥501 msec and of QTc increase of > 60 msec from baseline were significantly higher with the combination dabrafenib-trametinib (4% and 13%, respectively) compared with the trametinib (2% and 3%, respectively) and the dabrafenib (<1% and 3%, respectively) monotherapy populations. Grade 3 QTc (≥501 msec) concomitantly with >60 msec from baseline were reported as sporadic events (1%). The data presented suggests a marginal clinical relevance of the observed QT prolongation events in patients treated with trametinib monotherapy.

Haemorrhagic events: In the primary dataset, one event in each of the categories brain stem haemorrhage, cerebral haemorrhage, haemorrhage intracranial, gastric haemorrhage and haemoptysis was noted in the BRF113220 part C combination therapy population. In contrast, no bleeding SAEs are reported in the part C dabrafenib monotherapy population. All but one of the 9 fatal events in BRF113220 was considered unrelated to study drug by the investigator. However, upon review of the brief narratives, 2 additional cases concerning intracranial haemorrhage may well be suspected as related to study drug. An updated analysis listed 2 additional SAEs of GI haemorrhage (1 grade 3 and 1 grade 4), and 1 intracranial haemorrhage leading to permanent discontinuation of study drug, reported in BRF113220 randomised part C. In MEK114267, 2 additional SAEs of haemoptysis and 1 of haematoma were reported.

Rhabdomyolysis: there have been 5 documented cases of rhabdomyolysis (one grade 2 and four grade 3). Three of these occurred with trametinib monotherapy (1.4%) compared to no cases in the chemotherapy group in MEK114267. In one of these cases, rhabdomyolysis recurred on re-starting trametinib. The other two cases occurred in patients who received trametinib in combination with dabrafenib. In all 5 cases rhabdomyolysis was judged as being related to trametinib or combination treatment. In three of the cases treatment with trametinib had to be interrupted.

Serious adverse event / deaths / other significant events

Serious AEs

Trametinib monotherapy

SAEs were reported in 22% of patients in the TISS and 24% of the patients in the trametinib arm of MEK114267 study, whereas SAEs in the chemotherapy arm were reported in 20% of subjects. Cellulitis was the most frequent SAE in the TISS followed by pulmonary embolism, anaemia, dyspnoea, pneumonitis, vomiting, dehydration and erysipelas. Pyrexia, cholecystitis, and anaemia were the most common SAEs in subjects treated with chemotherapy. SAEs that were considered by the investigator to be related to study drug occurred in 33 patients (10%) in the TISS, in 26 subjects (12%) in the MEK114267 trametinib arm and in 11 subjects (11%) in the chemotherapy arm.

Combination Trametinib-Dabrafenib

In addition to the standard definition of SAEs, the BRF113220 study protocol mandated that the following events were to be reported as SAEs, regardless of whether the patients were hospitalised: SCC; LVEF decreases meeting protocol-defined stopping criteria; CSR or RVO, valvular toxicity meeting protocol-defined stopping criteria; new primary cancers; and pyrexia accompanied by hypotension and/or rigors/chills. The reported incidence of SAEs was significantly higher in the Part C 150/2 combination group (62%) compared to the uTISS (22%) and DISS (30%), this difference might be partly explained by the differences in SAE criteria used for the different safety populations.. The overall SAE profile of the combination trametinib-dabrafenib was consistent in the Part C 150/2 and the Pooled 150/2 populations, as well as in the DISS and the Part C dabrafenib monotherapy populations. In the Part C 150/2 combination group, pyrexia (25%) and chills (18%) were the most commonly reported AEs (mostly considered drug related), followed by dehydration, Ejection Fraction decreased, SCC, pulmonary embolism and renal failure (4% each).

In the MEK115306 study overall, 35% of patients in the combination arm reported SAEs. The most common AEs reported were pyrexia (15%) and chills (4%).

Deaths

Trametinib monotherapy

At the data cut-off date of study MEK114267, 84 patients (40%) in the trametinib arm had died compared with 50 patients (50%) in the chemotherapy arm. Of note, 31 patients enrolled in the chemotherapy arm died following crossover to trametinib, mostly due to disease progression.

At the data cut-off date for the TISS, 157 subjects (48%) treated with trametinib had died, of which 37 (11%) within 28 days after last dose of study treatment. Disease progression was the reason for death in 147 of the 157 cases. A total of 5 patients in the TISS died due to 6 fatal SAEs (1 gastrointestinal fistula, 1 myocardial infarction, 1 renal failure, 1 hepatic and renal failure, 1 infected skin ulcer, 1 death not otherwise specified), compared with 2 patients treated with chemotherapy in the MEK114267 study (pneumonia and pseudomembranous colitis). All except one of the fatal SAEs (renal failure in Subject 402007) were considered not drug-related. The fatal SAE in MEK113583 (gastrointestinal fistula) was reported as a post-therapy fatal SAE. One fatal SAE was reported in the Crossover Population of study MEK114267 and was not considered drug-related.

By analysis of all fatal SAEs across the trametinib program (including 1486 patients) using 26 September 2012 as cut-off date, 74 fatal SAEs have been reported, of which 63 considered not-related to study drug and with cause of death consistent with what observed in patients with metastatic cancer and late stage AML. Of the 11 fatal SAEs considered drug-related, one was reported in the chemotherapy arm of a randomized phase II study. In 5 of the remaining 10 cases, a cardiac etiology related to trametinib cannot be excluded. In other 3 cases, interstitial lung disease or pneumonitis were reported as fatal SAEs, two of which observed in patients treated with trametinib in combination with gemcitabine. Moreover, based on a preliminary review, 9 cases of sudden death or cardiac arrest related to study drug were identified.

Finally, additional cases of fatal SAEs were reported in the ongoing phase II study MEK114653, comparing trametinib versus docetaxel in patients with NSCLC, a trial that has been early stopped following recommendation of the internal safety review committee due to lack of efficacy associated to unfavourable toxicity associated with trametinib, essentially due to the higher rate of fatal SAEs observed in the trametinib arm (8 patients) versus none in the docetaxel arm. However, only in one of such cases death was considered possibly related to trametinib. Of note incidence of specific SAEs reported in study MEK114653 (pneumonia and dyspnoea) was higher than observed in the TISS.

Combination Trametinib-Dabrafenib

The incidences of death events and deaths ≤ 28 days after last dose of study drug were higher in the uTISS (48% and 11%, respectively) and DISS (47% and 15%) compared to Part C 150/2 (33% and 4%) and Pooled 150/2 (25% and 9%) populations. In the great majority of cases death was related to underlying disease; incidence of death due to SAE possibly related to study treatment was low (≤2%) and similar in all treatment arms. Nine patients in study BRF113220 reported fatal SAEs, all considered not related to study drug with the exception of a case of ventricular arrhythmia, where relation with study medication could not be excluded.

In the MEK115306 study four fatal SAEs (2%) were reported for the trametinib/dabrafenib combination treatment. None of these events were deemed related to the study therapy by the investigator. No fatal events were reported in the dabrafenib monotherapy arm.

Laboratory findings

Trametinib monotherapy

In general frequency of haematological and biochemical abnormalities was very similar between the TISS and the trametinib arm of study MEK114267. In the TISS the most commonly observed haematological abnormalities were: haemoglobin decreased (40%, 4% grade ≥3), platelet count decreased (19%, <1% grade ≥3), neutrophil count decreased (14%, 0% grade ≥3). Similar percentages were observed in the trametinib arm of MEK114267 study and were different compared to the chemotherapy arm (anaemia 27%, 3% grade ≥3; neutrophil count decreased 23%, 5% grade ≥3; platelet count decreased 21%, 2% grade ≥3).

The most common (>40% patients overall) biochemical abnormalities were AST increase (63%, 4% grade ≥3 in the TISS and trametinib arm of MEK114267 study versus 16%, 1% grade ≥3 in the chemotherapy arm of study MEK114267), ALT increase (36%, 3% grade ≥3 versus 20%, 3% grade ≥3, respectively), hypoalbuminemia (53%, 4% grade ≥3 versus 24%, 1% grade ≥3, respectively), hyperglycaemia (50%, 2% grade ≥3 versus 51%, 1% grade ≥3, respectively), and hypoglycaemia (13%, <1% grade ≥3 versus 3%, 0% grade ≥3, respectively).

Combination Trametinib-Dabrafenib

The combination of trametinib with dabrafenib in the Part C 150/2 of the BRF113220 study resulted in an increased incidence of haematological and biochemical abnormalities. In particular, an increased incidence of anaemia (55%, Grade 3/4: 4%/0), lymphocytopenia (55%, Grade 3/4: 16%/5%), neutrophil count decreased (55%, Grade 3/4: 7%/5%), platelet count decreased (31%, Grade 3/4: 2%/2%) were observed compared with the updated Trametinib ISS (uTISS, anaemia [40%, Grade 3/4: 4%/0], lymphocytopenia [15%, Grade 3/4: 3%/<1%], neutrophil count decreased [14%, Grade 3/4: 0/0], platelet count decreased [19%, Grade 3/4: 0/<1%]), and the Dabrafenib ISS (DISS, anaemia [31%, Grade 3/4: 2%/0], lymphocytopenia [25%, Grade 3/4: 7%/<1%], neutrophil count decreased [13%, Grade 3/4: <1%/<1%], platelet count decreased [8%, Grade 3/4: <1%/<1%]) populations.

Regarding biochemical abnormalities, in the all population treated with combination trametinib-dabrafenib (365 pts) an increased incidence of hyponatraemia (48%, Grade 3/4: 11%/<1%), potassium abnormalities and increased alkaline phosphatase (60%, Grade 3/4: 5%/0) was observed compared with uTISS and DISS populations, with hyperglycaemia, ALT/AST increase, hyperglycaemia, phosphorus abnormalities and hypomagnesaemia being also frequently observed.

Safety in special populations

No studies in paediatric populations have been completed to date with trametinib as monotherapy or in combination with dabrafenib, therefore no data on safety of trametinib and dabrafenib in paediatric patients are available. No data are available on the safety of the drugs in pregnant women. No analyses were conducted by race, as all patients enrolled in the studies were classified as white (100%). The lack/paucity of data in paediatric patients, pregnant women, races other than White and patients ≥ 75 years old are reflected in the SmPC.

Hepatic impairment

All studies performed with trametinib allowed inclusion of patients with mild hepatic impairment (bilirubin ≤1.5x ULN, ASAT/ALAT ≤2.5 or 5x ULN). In the 64 patients (13%) included in the population PK analysis, CL/F of trametinib was only 2% altered, a value which is not considered clinically relevant. The Applicant has provided data regarding the toxicity of trametinib, alone or in combination with dabrafenib, in patients with mild hepatic impairment compared with patients with normal liver function.

Regarding the toxicity of trametinib when given as monotherapy in patients with mild hepatic impairment, an increased incidence (>10%) of fatigue, dyspnoea and AST increased was observed compared with patients with normal liver function. However, the incidence of serious adverse events, withdrawal from study treatment due to AE, and dose reductions was similar between the two groups evaluated.

Regarding the toxicity of trametinib when given in combination with dabrafenib, events like nausea, vomiting, oropharyngeal pain, urinary tract infection, rash-generalized, and muscular weakness as well as serious AEs in general were more frequently (>10%) reported in patients with mild hepatic impairment compared with subject with normal hepatic function. However, other events including pyrexia, chills, arthralgia, diarrhoea, rash, cough, visual disorders and night sweats, as well withdrawal due to AEs, occurred more often in normal hepatic function patients compared to mild hepatic impaired patients. Frequency of rash and of AEs leading to dose reductions was similar between the two sub-population.

Renal impairment

An analysis of Adverse Events differentiated by patients with normal or impaired renal function has been performed. With the exception of few adverse events, including peripheral oedema, constipation, alopecia, pruritis, abdominal pain, pain in extremity and erythema, which were more frequently observed in patients with moderate renal impairment compared with mild or normal renal function, the toxicity of trametinib appears similar. Moreover, the limited number of patients with moderate renal impairment treated with trametinib (27 subjects) in the study performed to date, limits the reliability of the above mentioned findings. Therefore, no firm conclusions can be drawn on side effects of Mekinist in subjects with GFR < 60 ml/m.

The PK data available confirms no significant effect of renal impairment on the PK and safety of trametinib.

Age

Trametinib monotherapy

In the TISS, the majority of patients (76% [249]) were aged <65 years at baseline; 24% [80 pts] were ≥65 years, of which 16% [13 pts] were ≥75 years. Some events (e.g., rash [60% vs 51%], fatigue [36% vs 25%], nausea [32% vs 25%], dermatitis acneiform [24% vs 19%], vomiting [22% vs 14%], dry skin [18% vs 14%], abdominal pain [14% vs 11%], headache [14% vs 5%]) appear to be more frequently reported in patients <65 years, whereas other events (e.g., oedema peripheral [30% vs 44%], constipation [17% vs 23%], decreased appetite [12% vs 15%], pain in extremity [6% vs 11%]) were more frequently observed in among subjects ≥65 years. However, incidence of AEs, SAEs, and drug-related AEs was similar between the two study arms. A lower proportion of subjects aged <65 years had AEs leading to permanent discontinuation of study drug, dose reduction and dose interruption. Subjects aged >75 years had higher proportions of all types of AEs compared with the other age groups. However, they represent a small subgroup of the population treated (13 patients).

Combination Trametinib-Dabrafenib

In the Pooled 150/2 population, 160 patients were < 65 years whereas 42 patients were ≥65 years, of which 19 patients were ≥75 year old. Overall, incidence of drug-related AEs (90% vs 95%), SAEs (36% vs 48%), AEs leading to permanent discontinuation (7% vs 14%), dose reduction (44% vs 64%) or interruption (60% vs 71%), fatal SAEs (1% vs 12%), as well as specific AEs like fatigue (34% vs 52%), diarrhoea (26% vs 31%), oedema peripheral (16% vs 33%), constipation (15% vs 33%), dry skin (9% vs 19%), and anaemia (15% vs 24%) were more frequently reported in patients ≥65 years. In contrast, in patients < 65 years an increased incidence of rash (29% vs 19%), arthralgia (29% vs 21%), and headache (28% vs 24%) was observed. Of note, overall the frequencies of Grade 3 and 4 AEs were similar in the two age groups, but the incidence of Grade 3 or 4 SCC was higher in the ≥65 year old group (1% vs10%).

Gender

According to the data provided, a trend versus a slight increase of specific AEs could be observed in females compared to males treated with trametinib or the combination trametinib-dabrafenib, which could be partly justified by the difference in trametinib exposure observed by gender and weight. In the TISS, incidence of SAEs was higher in females than males (14% vs 8%, respectively), and frequency of several AEs (e.g. diarrhoea [56% vs 44%], oedema peripheral [39% vs 29%], nausea [34% vs 28%], vomiting [26% vs 16%], constipation [21% vs 17%], dry skin [21% vs 15%], pruritus, abdominal pain [18% vs 10%], headache [15% vs 9%]) was higher in female. However, other AEs (e.g., rash, fatigue, dermatitis acneiform) were more frequently reported in males.

Safety related to drug-drug interactions and other interactions

No specific drug-drug interaction study has been performed with trametinib. As trametinib is metabolized predominantly via hydrolytic enzymes, its pharmacokinetics is unlikely to be affected by drug-drug interactions. Moreover, based on in vitro and in vivo data, interaction via CYP enzymes and transporters is unlikely. Trametinib has been given in combination with other compounds (e.g., gemcitabine, dabrafenib) in several clinical studies but, with the exceptions of the combination with dabrafenib, no other data are available regarding the safety of the drug in other combinations. A relevant PK interaction has been observed when trametinib was administered with food, therefore administration of the drug in fasted condition is currently recommended.

Clinically relevant PK-PD interactions via induction of cytochrome P450 isoenzyme (CYP) 3A4-mediated metabolism and of other enzymes including CYP2B6, CYP2C8, CYP2C9, and CYP2C19 mediated by dabrafenib have been demonstrated. Therefore co-administration of dabrafenib with compounds metabolized by such enzymes (e.g., hormonal contraceptives, warfarin, dexamethasone) should be avoided. Moreover, as dabrafenib is primarily metabolized by CYP2C8 and CYP3A4 strong inhibitors or inducers of such enzymes should be avoided.

Administration of dabrafenib and trametinib in combination had no clinically relevant effect on the exposure of trametinib or of dabrafenib monotherapy.

Discontinuation due to adverse events

Trametinib monotherapy

Overall, 10% of subjects in the TISS, and 12% and 9% of subjects in the trametinib and chemotherapy arms of study MEK114267, respectively, had AEs that led to permanent discontinuation of study drug. Each AE leading to permanent discontinuation of trametinib monotherapy occurred in 2 or fewer subjects with the exception of pneumonitis (4 cases in both the trametinib arm of MEK114267 and the TISS), and ALT increased (3 cases in the trametinib arm of MEK114267). Flushing and peripheral sensory neuropathy led to discontinuation in 2% of subjects in the chemotherapy arm of MEK114267 versus none in the trametinib arm. Several patients had also AEs related to LVEF decreases that met the protocol-mandated study drug stopping criteria.

The proportion of patients reporting AEs leading to dose reductions and AEs leading to dose delays/interruptions was similar in the TISS (26% and 36%, respectively) and in the trametinib arm of study MEK114267 (32% and 38%, respectively). The most common AEs (≥2% of subjects) leading to dose reduction in the TISS were rash (8%), decreased ejection fraction (2%) and dermatitis acneiform (2%). In study MEK114267 the most common AEs (≥2% of subjects) leading to dose reduction in the trametinib arm were rash (10%), and decreased ejection fraction (3%), the incidence of which was higher compared with the chemotherapy arm (both 0%, respectively). Each AE leading to dose reduction in the chemotherapy arm occurred in 1 subject, with the exception of neutrophil count decreased (2%).

The most common AEs (≥2% of subjects) leading to dose interruptions in the TISS were rash (9%), diarrhoea (5%), ejection fraction decreased (3%), oedema peripheral (2%), ALT increased (2%), left ventricular dysfunction (2%), fatigue (2%), pyrexia (2%), cellulitis (2%), dehydration (2%), nausea (2%) and vomiting (2%). Similar percentages were observed in the trametinib arm of study MEK114267. With the exception of fatigue, the incidence of all these most common events was higher compared with the chemotherapy arm. The most common AEs leading to dose interruptions in the chemotherapy arm were platelet count decreased (4%), neutropenia (3%), fatigue (2%), anaemia (2%), pancytopenia (2%), and peripheral sensory neuropathy (2%).

Combination Trametinib-Dabrafenib

The frequency of AEs leading to permanent discontinuation of study drug was similar between the Part C 150/2 group (9%) and the uTISS population (10%), but higher than the DISS population (3%). Two of the 5 subjects who discontinued study drug permanently due to an AE discontinued due to pyrexia.

The proportion of patients reporting AEs leading to dose reductions was higher in the Part C 150/2 population (49%) compared with the TISS (26%) and the DISS (17%), and was essentially due to pyrexia (35%), followed by chills and nausea (9% each), vomiting and decreased ejection fraction (7% each).

The proportion of patients reporting AEs leading to dose interruptions was higher in the Part C 150/2 population (67%) compared with the uTISS (36%) and the DISS (33%), and was essentially due to pyrexia (42%), followed by chills (22%), decreased ejection fraction (9%), arthralgia, diarrhoea, fatigue, nausea, vomiting and neutropenia (7% each). Importantly, no subjects had dose interruptions for AEs of PPE in the Part C 150/2 group (in contrast with 10 cases (2%) in the DISS population) as well as no patients had AEs of rash leading to dose interruption in the Part C 150/2 group.

For patients receiving treatment with trametinib in combination with dabrafenib in the MEK115306 study, when compared with the dabrafenib/placebo arm, AEs leading to dose reduction or interruption were reported in 45% and 24% of patients, respectively. The most common event leading to dose modification (reduction, interruption and permanent discontinuation) was pyrexia. Permanent discontinuation due to an AE was reported in 9% of the patients in the combination arm vs 5% in the dabrafenib monotherapy arm. AEs leading to dose reduction were reported in 24% for the combination arm and 13% for the monotherapy arm.

2.6.1. Discussion on clinical safety

The safety profile of trametinib as monotherapy was consistent across studies: rash and other skin events, gastrointestinal (e.g. diarrhoea, nausea vomiting) and ocular toxicities, peripheral oedema, and hypertension were prominent and dose limiting, whereas hematologic toxicity was very limited.

Trametinib as monotherapy appears to be less well tolerated compared with chemotherapy (i.e. paclitaxel, dacarbazine). However, the analysis is hampered by the difference in treatment duration observed between the two study arms. In addition, the dose of dacarbazine used in the pivotal trial (1000 mg/m2) is higher than the dose commonly used in clinical practice (850 mg/m2) and recommended in the SmPC of most EU countries.

Safety data obtained from phase I and II clinical study indicate that the trametinib-dabrafenib 150/2 mg combination is less well tolerated than both drugs given as monotherapy (uTISS and DISS) showing a higher rate of AE that have led to dose mitigation or interruption of treatment, than ‘monotherapy’ dabrafenib/placebo. Also the rate of SAE was higher in the dabrafenib/trametinib combination. A comparison of updated AE of special interest between study arm in MEK115306 shows that hepatic disorders, diarrhoea, hypertension, oedema, pyrexia, hyperglycaemia and neutropenia were all more commonly seen with combination therapy while CuSCC was reported more commonly in the dabrafenib monotherapy arm. However, several peculiar toxicities observed with the drugs given as monotherapy, were observed with a frequency lower than it would have been expected, probably due to mutual inhibition achieved by combination therapy of paradoxical activation of RAF, RAS or MEK –MAP kinase pathways caused by single selective inhibition of BRAF or MEK. The most frequently reported AEs with the combination treatment included pyrexia (71%), chills (58%), fatigue (53%), nausea (44%), and vomiting (40%), and the incidence was significantly higher compared with the trametinib and dabrafenib monotherapy. The incidences of rash (27%) and diarrhoea (36%) were 1.5 to 2 fold lower compared with the trametinib monotherapy population (58% and 49%, respectively).

In general the safety results of the MEK115306 study confirm the toxicity profile of the trametinib-dabrafenib combination treatment as determined in the BRF113220 study. However, the evaluation of the toxicity profile of the combination trametinib-dabrafenib is hampered by the patients treated by relatively short follow-up.

Pyrexia has been reported in clinical trials with trametinib as monotherapy and in combination with dabrafenib. The incidence and severity of pyrexia are increased with the combination therapy.

LVEF reduction has been reported with trametinib, when used as monotherapy or in combination with dabrafenib. In clinical trials, the mean time to onset of left ventricular dysfunction and LVEF decrease was between 2 to 4 months. Therefore, trametinib should be used with caution in patients with impaired left ventricular function. Safety in patients with left ventricular dysfunction, New York Heart Association Class II, III, or IV heart failure, acute coronary syndrome within the past 6 months, clinically significant uncontrolled arrhythmias, and uncontrolled hypertension, is unknown as these patients were excluded from clinical trials. As a consequence, LVEF should be evaluated in all patients prior to initiation of treatment with trametinib, one month after initiation of therapy, and then at approximately 3 monthly intervals while on treatment (see section 4.4 of the SmPC). Trametinib should be interrupted in patients who have an asymptomatic, absolute decrease of > 10 % in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal (LLN). With Grade 3 or 4 left ventricular cardiac dysfunction or if LVEF does not recover trametinib should be permanently discontinued (see section 4.2 of the SmPC).

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 labelling of patient populations at highest risk for developing these toxicities and to provide evidence-based dose modification and monitoring recommendations (see RMP).

The applicant also committed to conduct a study (MEK114655) to evaluate the effect of trametinib on QTc in patients with solid tumours and to provide the results by Q4 2015 (see RMP).

Peripheral oedema was reported in around 40% of patients treated with trametinib monotherapy compared with 5% of patients treated with chemotherapy. In about 50% of cases oedema was associated with left ventricular dysfunction (see section 4.8 of the SmPC).

Elevations in blood pressure have been reported in association with trametinib and trametinib in combination with dabrafenib, in patients with or without pre-existing hypertension. Blood pressure should be measured at baseline and monitored during treatment with trametinib, with control of hypertension by standard therapy as appropriate (see section 4.4 of the SmPC).

Patients treated with trametinib may develop ILD or pneumonitis. Trametinib should be withheld in patients with suspected ILD or pneumonitis, including patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. Trametinib should be permanently discontinued for patients diagnosed with treatment-related ILD or pneumonitis (see sections 4.2, 4.4 and 4.8 of the SmPC).

Skin-related events essentially consisted of rash and dermatitis acneiform. In clinical studies with trametinib, rash has been observed in about 60 % of patients. The majority of these cases were Grade 1 or 2 and did not require any dose interruptions or dose reductions (see sections 4.2 and 4.4 of the SmPC). Supportive care guidelines regarding dose adjustment depending on the severity of the rash have been included in section 4.2 of the SmPC.

Disorders associated with visual disturbance, including RPED and RVO, have been observed with trametinib as monotherapy. Symptoms such as blurred vision, decreased acuity, and other visual phenomena have been reported in the clinical trials with trametinib. The safety of trametinib in subjects with predisposing factors for retinal vein occlusion (RVO), including uncontrolled glaucoma or ocular hypertension, uncontrolled hypertension, uncontrolled diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes, has not been established. A prompt ophthalmological assessment is recommended if patients report new visual disturbances, such as diminished central vision, blurry vision or loss of vision at any time while on trametinib therapy. If RPED is diagnosed, dose modification should be undertaken. In patients who are diagnosed with RVO, treatment with trametinib should be permanently discontinued (see sections 4.2, 4.4 and 4.8 of the SmPC).

Hepatic adverse events have been reported in clinical trials with trametinib. It is recommended that patients receiving treatment with trametinib have liver function monitored every four weeks for 6 months after treatment initiation with trametinib (see sections 4.4 and 4.8 of the SmPC).

Renal failure was reported with trametinib monotherapy. Renal failure AEs were associated with pyrexia or diarrhoea in the majority of cases, where dehydration could be a contributing factor.

Haemorrhagic events, including major haemorrhagic events, have occurred in patients taking trametinib. The potential for these events in patients with brain metastases or low platelets (< 100,000) is 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. Haemorrhage has therefore been included in the sections 4.4 and 4.8 of the SmPC. In addition “haemorrhagic events” has been added as an important risk for trametinib in the RMP.

Rhabdomyolysis has been reported in patients taking trametinib. In some cases, patients were able to continue trametinib. In more severe cases hospitalisation, interruption or permanent discontinuation of trametinib was required. Signs or symptoms of rhabdomyolysis should warrant an appropriate clinical evaluation and treatment as indicated (see section 4.4 of the SmPC and RMP).

Based on available data, a possible trend towards a slightly worse tolerability of trametinib in patients with mild hepatic impairment could be hypothesized but the limited number of patients treated does not allow drawing any firm conclusion over this issue. No dosage adjustment is required in patients with mild hepatic impairment. There are no clinical data in patients with moderate or severe hepatic impairment; therefore, the potential need for starting dose adjustment cannot be determined and administration of trametinib should be undertaken with caution in those patients (see section 4.4 of the SmPC). As metabolism and biliary excretion are the primary routes of elimination of trametinib, administration of trametinib should be undertaken with caution in patients with moderate to severe hepatic impairment. The Applicant commits to provide post-approval the results of a planned pharmacokinetic trial to determine the appropriate dose of trametinib in patients with hepatic impairment. The study report should be available by Q4 2017.

As the PK data available appear to confirm no significant effect of renal impairment on the PK and safety of trametinib, no dosage adjustment is required in patients with mild or moderate renal impairment. There are no data with trametinib in patients with severe renal impairment; therefore, the potential need for starting dose adjustment cannot be determined. Trametinib should be used with caution in patients with severe renal impairment.

More frequent dose adjustments may be required in patients > 65 years of age.

In clinical trials with trametinib one case of accidental overdose was reported; a single dose of 4 mg. No AEs were reported following this event of trametinib overdose (data not shown). There is no specific treatment for overdose and in case overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary (see section 4.9 of the SmPC).

Trametinib has minor influence on the ability to drive or use machines. The clinical status of the patient and the adverse reaction profile should be borne in mind when considering the patient's ability to perform tasks that require judgment, motor and cognitive skills. Patients should be made aware of potential for fatigue, dizziness or eye problems that might affect these activities (see section 4.7 of the SmPC).

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

2.6.2. Conclusions on the clinical safety

The toxicity of trametinib includes rash and other skin events, gastrointestinal (e.g., diarrhea, nausea vomiting) and ocular toxicities, peripheral oedema, and hypertension, whereas hematologic toxicity was very limited. The AEs were usually mild or moderate in severity, and toxicity was usually manageable, at least when adequate monitoring of patients was performed and established guidelines were followed. Due to the peculiarity of the AEs observed, specific and periodical monitoring (ophtalmological, dermatological, cardiological [LVEF/ECG] evaluation) is required in order to allow prevention and early management of clinically relevant consequences.

In study MEK115306, all SAEs except cutaneous squamous cell carcinoma had a higher frequency (>2%) in the combination arm than in the dabrafenib arm.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

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

The PRAC considered that the risk management system version 8.0 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 40: Summary of Safety Concerns

Important identified risks	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)
	Pneumonitis
	Hepatic events (AST, ALT, increased)
	Hypertension
	Oedema events (e.g. oedema peripheral)
	Hypersensitivity
	Rhabdomyolysis
	Haemorrhagic events
Important potential risks	Off-label use: in resectable/resected melanoma (adjuvant treatment), in nonmelanoma 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, use in combination with other anti-cancer agents, or when non-validated tests are used
	Hepatic failure
	Impaired female fertility
	Developmental toxicity
Missing information	Use in patients with reduced cardiac function or symptomatic Class II, III, or IV heart failure (NYHA functional classification system)
	Safety in patients with severe renal impairment
	Safety in patients with moderate to severe hepatic impairment
	Use in Non-White population
	Pregnancy and risks in breast-feeding
	Use in paediatric population (children less than 18 years)
	Risks in patients with ECOG 2-4
	Safety in elderly (≥65 years) patients

	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), treatment refractory hypertension (blood pressure of systolic> 140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by anti-hypertensive therapy)
	Safety in patients with history of retinal vein occlusion or central serous retinopathy (reclassified as Retinal Pigment Epithelial Detachment, RPED)
	Safety in patients with history of pneumonitis or interstitial lung disease
	Long-term treatment (>12 months)
	Drug-drug interactions (i.e., Enzymes responsible for the hydrolytic cleavage of trametinib, 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)

Pharmacovigilance plans

Table 41: On-going and planned studies in the PhV development plan

Cat	Description of activity (or study title if known)	Milestone(s)	Due Date(s)*
3	**MEC116354 Hepatic Impairment** NCI Sponsored Phase I and PK Study	Protocol submission	3Q2013
		Study start	2Q2014
		Study finish	3Q2016
		Final report complete	4Q2017
3	**Annual Reports for Cardiomyopathy-related adverse reactions** 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 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.	Interim reports submitted annually through 2020	4Q2020
3	**GSK1120212B: *In Vitro* Phototoxicity Assay with 3T3 Cells** An *in vitro* assay to better characterise the risk of photosensitivity reactions	Study start	2Q2014
		Final report complete	1Q2015
3	**A repeat study to investigate the enzymes responsible for the hydrolytic cleavage of trametinib**	Study start	2Q2014
		Study finish/Final report complete	1Q2015
3	**Studies investigating the potential for saturation of P-gp and BCRP using MDCKII-MDR1 and MDCKII-BCRP cell lines at clinically relevant concentrations**	Study start	2Q2014
		Study finish/Final report complete	1Q2015
3	**Studies determining whether trametinib is a substrate of OATP1B1 and OATP1B3 and whether trametinib is an inhibitor of OCT2, OAT1, or OAT3**	Study start	2Q2014
		Study finish/Final report complete	1Q2015

Abbreviations: NCI= National Cancer Institute; PK=pharmacokinetic; 1Q = quarter 1; 2Q = quarter 2; 3Q= quarter 3; 4Q = quarter 4
*Timelines may shift based on the actual start date of the respective study(ies)

*Category 1 are imposed activities considered key to the benefit risk of the product; Category 2 are specific obligations; Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Risk minimisation measures

Table 42: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
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 PL • 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
Diarrhoea	• ADR 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
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 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)	• 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 should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products	None
Pneumonitis	• Warning in product labelling • ADR in product labelling • Information for patients in PL • 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
Hepatic events (e.g., AST and ALT increased)	• Warning in product labeling • ADR in product labelling • Information for patients in PIL	None

	• Prescription only medicine • Treatment with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products	
Hypertension	• ADR 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
Oedema events (e.g., oedema peripheral)	• ADR 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
Hypersensitivity	• Contraindication in product labelling • ADR 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
Rhabdomyolysis	• Warning and ADR in product labelling • Treatment with trametinib 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 • Treatment with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products	None
Important potential risks		
Off-label use in resectable /resected melanoma (adjuvant treatment), in nonmelanoma 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, use 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 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 • Treatment with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products	None

Impaired Female Fertility	• 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
Developmental Toxicity	• 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 information		
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 PL • 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
Safety in patients with severe renal impairment	• Information in product labelling • 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
Safety in patients with moderate to severe hepatic impairment	• Information in product labelling • 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
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 should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	None
Pregnancy and risks in breastfeeding	• Information in product labelling • Information for patients in PL • 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 paediatric population (children <18 years)	• Information in product labelling • Information for patients in PL • 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 ECOG 2-4	• No data in this population is available • Prescription only medicine	None

	• Treatment with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.	
Safety in elderly (>65 years) patients	• Information in product labelling • Information for patients in PL • 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
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), treatment refractory hypertension (blood pressure of systolic> 140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by anti-hypertensive therapy)	• Information in product labelling • Information for patients in PL • 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
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 PL • 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
Safety in patients with history of pneumonitis or interstitial lung disease	• Information in product labelling • Information for patients in PL • 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
Long-term treatment (>12 months)	• Ongoing evaluation of adverse events in patients • 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
Drug-drug interactions (i.e., Enzymes responsible for the hydrolytic cleavage of trametinib, 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)	• Information in product labelling • 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

The CHMP endorsed this advice with the exception of one study which will contribute in addressing the missing information on patients with a history or evidence of cardiovascular risk (see below).

Cat	Description of activity (or study title if known)	Milestone(s)	Due Date(s)*
3	**MEK114655: QTc Study** A Study to evaluate the effect of trametinib on QTc in subjects with solid tumours	Final report complete	4Q 2015

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Trametinib monotherapy

The results of the PFS analysis in the ITT population of the MEK114267 pivotal study shows a statistically significant improvement in PFS (assessed by investigators) for trametinib monotherapy compared with chemotherapy (HR=0.45, 95% CI 0.33-0.63, p<0.0001, median PFS 4.8 vs 1.5 months, respectively).

The median OS was 15.6 months (95% CI; 14.0, 17.4) in the trametinib arm and 11.3 months (95% CI; 7.2, 14.8) in the chemotherapy arm. The hazard ratio (HR) was 0.78 (95% CI; 0.57, 1.06) with a p value of 0.09. ORR (according to IRC assessment) was also significantly higher with trametinib compared with chemotherapy (22% vs 8%, respectively, p=0.0100).

No benefit has been observed for trametinib when given sequentially after refractoriness to BRAF-inhibition in patients with melanoma harbouring BRAF V600 mutations. Although the caveats related to inter study comparison are acknowledged, the magnitude of the effect in terms of ORR observed with trametinib as monotherapy in treatment naïve melanoma patients appears to be lower than the effect observed with selective BRAF-TKi (e.g. vemurafenib, dabrafenib.

In the studies performed to date with trametinib monotherapy the majority of melanoma patients presented BRAF V600E mutations. Whilst the ORR appears lower in patients with tumours expressing the V600K mutation, efficacy in terms of PFS seems to be essentially similar comparing V600E and V600K. The CHMP concluded that there was enough evidence to support a broader indication of “V600 mutation” and not to restrict the indication to BRAF V600E patient population.

Trametinib-Dabrafenib combination

The evidence of efficacy of trametinib in combination with dabrafenib in patients with unresectable or metastatic melanoma was initially based on the results of one phase I/II study (BRF113220) proposed as pivotal for this indication.

Confirmatory results from the phase III study MEK115306 comparing the combination dabrafenib-trametinib vs dabrafenib monotherapy have been submitted during the course of the procedure. The median PFS for the combination trametinib/dabrafenib arm was 9.3 months) compared to 8.8 months for the monotherapy dabrafenib. The HR for PFS as assessed by the independent review committee (IRC) was 0.78 (95% CI: 0.59, 1.04; p=0.067). For both arms median OS was not yet reached.

Uncertainty in the knowledge about the beneficial effects.

Trametinib-Dabrafenib combination

No data are available regarding the efficacy of the drug in races others than Whites (Blacks, Asian, etc.). Similarly, no data are available in paediatric patients and experience in patients > 75 years of age is limited. The lack of data has been reflected in the SmPC.

Risks

Unfavourable effects

The safety profile of trametinib as monotherapy was consistent across studies: rash and other skin events, gastrointestinal (e.g., diarrhoea, nausea vomiting) and ocular toxicities, peripheral oedema, and hypertension were prominent and dose limiting, whereas hematologic toxicity was very limited. Trametinib as monotherapy appears to be less well tolerated compared with chemotherapy (i.e. paclitaxel, dacarbazine). However, the analysis is hampered by the difference in treatment duration observed between the two study arms. Moreover, quality of life data did not show significant difference between the two study arms. In patients treated with the combination dabrafenib-trametinib, compared with the trametinib and dabrafenib monotherapy populations, an increased incidence of AEs leading to dose reduction, AEs leading to dose interruption, grade 3/4 AEs, and SAEs was observed. The most frequently reported AEs with the combination treatment included pyrexia (71%), chills (58%), fatigue (53%), nausea (44%), and vomiting (40%), and the incidence of such events was significantly higher compared with what observed with trametinib and dabrafenib monotherapy.

Headline results from the MEK115306 study with a median time on study treatment of 8 months for the combination arm and 7 months for the dabrafenib 'monotherapy arm', confirm the toxicity results obtained in the phase I/II BRF113220 study. Overall the safety profile as observed in MEK115306 show a higher rate of AE that have led to dose mitigation or interruption of treatment in the combination treatment as compared to monotherapy. Also the rate of SAE was higher in the dabrafenib/trametinib combination. A comparison of updated AEs of special interest between study arms in MEK115306 shows that hepatic disorders, diarrhoea, hypertension, oedema, pyrexia, hyperglycaemia and neutropenia were all more commonly seen with combination therapy while CuSCC was reported more commonly in the dabrafenib monotherapy arm.

Uncertainty in the knowledge about the unfavourable effects

There are limited/no data in paediatric patients, races other than White and patients ≥ 75 years old which was reflected in the SmPC and the RMP.

Available data indicate a possible trend towards a slightly worse tolerability of trametinib in patients with mild hepatic impairment but the limited number of patients treated does not allow drawing any firm conclusion on this issue. There are no clinical data in patients with moderate or severe hepatic impairment. The results of a pharmacokinetic trial to determine the appropriate dose of trametinib in patients with hepatic impairment will be available by Q4 2017.

Benefit-risk balance

Importance of favourable and unfavourable effects

In the context of unmet medical need for patients with metastatic melanomas harbouring BRAF V600 mutation, the results provided in terms of improved PFS and OS for trametinibare considered of clinical relevance. For trametinib monotherapy, cross study comparison shows that the PFS and OS benefit for trametinib appears to be comparable to what is reported for approved BRAF inhibitors (dabrafenib and vemurafenib).

Of note, the patient population included in the study was BRAF-inhibitor naïve. In another phase II study, no clinically relevant effect was observed with trametinib monotherapy in patients pre-treated with a BRAF inhibitor.

Regarding the combination trametinib-dabrafenib therapy, although the pharmacological rationale was considered justified, and early clinical data were considered promising, more comprehensive efficacy data from a phase III trial failed to confirm the magnitude and statistical significance of the effect. Both PFS and OS data are considered too immature to provide corroborating evidence of efficacy.

Trametinib as monotherapy, although associated with higher toxicity compared with paclitaxel, dacarbazine, was not associated with worsened quality of life. The AEs were usually mild or moderate in severity, and toxicity was usually manageable when adequate monitoring of patients was performed and established guidelines were followed.

Overall, albeit manageable, the toxicity of the combination was not negligible, with a higher rate of AEs that have led to dose mitigation or interruption of treatment in the combination treatment, a higher proportion of patients experiencing SAEs and hepatic disorders, diarrhoea, hypertension, oedema, pyrexia, hyperglycaemia and neutropenia more commonly seen with combination therapy.

Benefit-risk balance

The efficacy of trametinib monotherapy in the population of patients with BRAF V600 mutation positive melanoma has clearly been established in terms of PFS and OS in MEK14267 is robustly demonstrated when compared to chemotherapy. Although, trametinib monotherapy appears to be less well tolerated compared to chemotherapy (i.e. paclitaxel, dacarbazine), the AEs were usually mild or moderate in severity, and toxicity was usually manageable when adequate monitoring of patients was performed and established guidelines were followed. It is concluded that the benefit-risk balance for trametinib monotherapy is positive.

The proposed trametinib-dabrafenib combination treatment is supported by a strong biological rationale. However, based on early clinical data and immature phase III data, the efficacy has not been established.

Although the AEs of the combination therapy are generally manageable when safety guidelines are followed, in the absence of established efficacy the benefit-risk balance could not be considered to be positive. The applicant withdrew the combination indication from the applied indication.

Discussion on the benefit-risk balance

No head-to-head comparison of trametinib monotherapy with BRAF inhibitors could be conducted as no BRAF inhibitors were approved at the time the trametinib monotherapy phase 3 study started. Although the caveats related to indirect study comparison are acknowledged, the ORR observed with trametinib in BRAF V600 mutant melanoma patients appears lower than the ORR observed with BRAF inhibitors (i.e., vemurafenib, dabrafenib) in a comparable patient population. Nevertheless, there is no concern that patients have a risk to miss the opportunity of effective therapy by using trametinib instead of a BRAF inhibitor as first line treatment: the efficacy of a BRAF inhibition after MEK inhibition may still be apparent.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Mekinist in the treatment of “adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Trametinib monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy”

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 8 months following authorisation. Subsequently, 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.

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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that trametinib is qualified as a new active substance.