Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for trametinib (as dimethyl sulfoxide)

Proprietary Product Name: Mekinist

Sponsor: GlaxoSmithKline Australia Pty Ltd

March 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ADME	Absorption, Distribution, Metabolism, Excretion
AE	Adverse event
ATP	Adenosine triphosphate
BCRP	Breast cancer resistant protein
BCS	Biopharmaceutics Classification System
BIRC	Blinded and independent review committee
BW	Body weight
CHC	Child resistant closures
CHMP	Committee for Medicinal Products
CI	Confidence interval
CL	Clearance
CL/F	Oral clearance
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CSR	Clinical study report
CT	Computed tomography
DMSO	Dimethyl sulfoxide

Abbreviation	Meaning
DTIC	Dacarbazine
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
ERK	Extracellular signal-related kinase
EU	European Union
FDA	Food and Drug Administration
FTIH	First-time-in-human
GFR	Glomerular filtration rate
GI	Gastrointestinal
GIT	Gastrointestinal tract
GLP	Good Laboratory Practice
GLS	Generalised least square
GSK	GlaxoSmithKline
HPMC	Hydroxypropylmethylcellulose
HR	Hazard ratio
IC	Inhibitory concentration
ICF	Isometric contractile force
ICH	International Conference on Harmonisation
ISE	Integrated summary of efficacy
IV	Intravenous
KA	Keratoacanthomas
LDH	Lactate dehydrogenase
LFT	Liver function test
LVEF	Left ventricular ejection fraction
MAP-kinase	Mitogen-activated protein kinase

Abbreviation	Meaning
MEK	Mitogen-activated extracellular signal regulated kinase
MOA	Mechanism of action
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NOAEL	No observed adverse effect level
NR	Not reached
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PFS	Progression free survival
P-gp	human P-glycoprotein
PK	Pharmacokinetic
PopPK	Population pharmacokinetics
PR	Partial response
Q3wk	Every 3 weeks
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumours
RMP	Risk Management Plan
RR	Response rate
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SmPC	Summary of Product Characteristics
SRS	Stereotactic radiation
ULN	Upper limit of normal

Abbreviation	Meaning
US	United States

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	11 February 2014
Active ingredient:	trametinib (as dimethyl sulfoxide)
Product name:	Mekinist
Sponsor's name and address:	GlaxoSmithKline Australia Pty Ltd Level 4/436 Johnston Street ABBOTSFORD VIC 2067
Dose form:	Film coated tablets
Strengths:	0.5 mg, 1 mg and 2 mg
Container:	HDPE Bottle and CRC
Pack sizes:	7 or 30 tablets
Proposed therapeutic use:	*Mekinist as a monotherapy and in combination with dabrafenib is indicated for the treatment of patients with BRAFV600 mutation positive unresectable or metastatic Stage IV) melanoma.* *Mekinist as monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy (see Clinical trials).*
Route of administration:	Oral
Proposed dosage:	2 mg orally once daily as monotherapy. 2 mg orally once daily when given in combination with dabrafenib (150 mg twice daily).
ARTG number:	205917, 205918, 205919

Product background

Therapeutic options for unresectable and metastatic melanoma are limited. Chemotherapy including agents such as imidazole, carboxamide and carboplatin have limited efficacy with only 10 to 15% of patients achieving any degree of tumour regression. More recently

vemurafenib a selective Proto-oncogene B-Raf (BRAF) inhibitor has demonstrated a worthwhile clinical benefit and another agent ipilimumab a mono-clonal antibody that blocks the cytotoxic T-lymphocyte antigen CTLA-4 has demonstrated significant improvement in overall survival (OS) of patients with metastatic melanoma. Nevertheless the need for further agents of worthwhile activity is clear and recognising that 60% of cutaneous melanomas have specific mutations of the BRAF oncogene which activates Mitogen-activated Extracellular signal regulated Kinase (MEK) in a down-stream Mitogen-Activated Protein (MAP) kinase signalling cascade, by interfering with this pathway at the level of the MEK kinases represents an alternative and potentially clinically active treatment option for unresectable metastatic BRAF mutant melanoma with a different safety.

Trametinib is a reversible allosteric inhibitor of Mitogen-activated Extracellular signal regulated Kinase (MEK1 and MEK2)[1]. MEK is part of the RAS/RAF/MEK/ERK (that is, MAP kinase) pathway (Qi M and Elion EA, 2005[2]); differences in the roles of MEK1 and MEK2 in this pathway are not well understood[3]. Derangements of this MAP kinase cascade are implicated in many cancers, particularly melanoma.

Treatment of advanced melanoma has changed with availability of ipilimumab (an anti-CTLA-4 antibody that enhances T-cell mediated immunity), vemurafenib (a BRAF inhibitor) and dabrafenib (a BRAF inhibitor approved in Australia in August 2013).

- Ipilimumab is indicated as monotherapy in patients with unresectable or metastatic melanoma who have failed or are intolerant to prior therapy.
- Vemurafenib is indicated in patients with unresectable Stage IIIC or Stage IV metastatic melanoma positive for BRAF V600 mutation.
- Dabrafenib is indicated for the treatment of patients with BRAF V600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma.

Use of vemurafenib or dabrafenib is strongly discouraged in wild-type BRAF melanoma. Preclinical models show BRAF inhibitors can enhance the MAPK pathway in tumour cells with wild-type BRAF and upstream RAS mutations[4]. 20% of metastatic melanomas may have NRAS mutations – these and BRAF mutations are usually mutually exclusive (Jakob JA et al. 2012[5]).

This is a new submission to seek registration for Trametinib as monotherapy and in combination with Dabrafenib for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic (Stage IV) melanoma.

Regulatory status

Mekinist was designated an orphan by the Therapeutic Goods Administration (TGA) on 1 June 2012 for treatment of patients with BRAF V600 mutation-positive unresectable or metastatic (Stage IV) melanoma.

[1] Half maximal inhibitory concentration (IC50) for MEK1 0.7 nM, for MEK2 0.9 nM; somewhat weaker binding to phosphorylated MEK1 and MEK2 (13.2 and 10.7 nM respectively)
[2] Qi M and Elion EA, 2005, MAP kinase pathways. J Cell Science 118 (16): 3569-3572
[3] For example, one paper (Skarpen et al 2008) suggests MEK1-activated ERK2 accumulates in the nucleus and induces proliferation, but that MEK2-activated ERK2 is retained in the cytoplasm and promotes survival – but both attributes are hallmarks of cancerous cells.
[4] http://www.cancer.gov/cancertopics/pdq/treatment/melanoma/HealthProfessional/page9
[5] Jakob JA, Bassett RL Jr, Ng Cs, et al. 2012, NRAS mutation status is an independent prognostic factor in metastatic melanoma. Cancer;118(16):4014-23

USA. Trametinib was approved by the Food and Drug Administration (FDA) as monotherapy and combination therapy (dabrafenib/trametinib). The full indications for trametinib are included in the US Product Information (PI) as:

> *Mekinst™ as a single agent is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test [see Clinical Studies (14.1)].*
>
> *Mekinist, in combination with dabrafenib, is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test. This indication is based on the demonstration of durable response rate [see Clinical Studies (14.1)]. Improvement in disease-related symptoms or overall survival has not been demonstrated for MEKINIST in combination with dabrafenib.*

Mekinist is not indicated for the treatment of patients who have received prior BRAF inhibitor therapy.

EU. A submission was made in the EU for monotherapy and combination therapy on 8 February 2013. As of 21 August 2013, it has not been approved by the European Medicines Agency (EMA).

Product Information

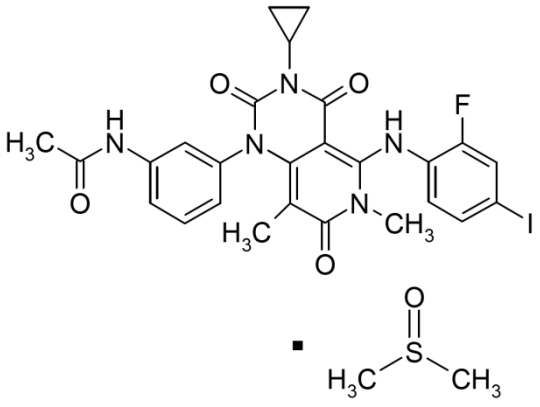
The approved PI current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Trametinib is N-[3-[3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-3,4,6,7-tetrahydro-6,8-dimethyl-2,4,7-trioxopyrido[4,3-d]pyrimidin-1(2H)-yl]phenyl]-acetamide. Trametinib is not chiral and does not show isomerism. The drug substance is the 1:1 dimethyl sulfoxide (DMSO) solvate. The structure of trametinib DMSO is shown in Figure 1.

Figure 1: Structure of trametinib dimethyl sulfoxide



trametinib dimethyl sulfoxide
Company code: GSK1120212B (trametinib solvate)
GSK1120212A or GSK1120212 (trametinib)

C26H23FIN5O4.C2H6OS MW: 615.39 (unsolvated)

The calculated basic pKa is 0.25 (acetamide): the absence of readily ionisable groups precludes the formation of stable and crystalline salts. The calculated partition coefficient of trametinib DMSO is 4.99 (lipophilic).

Trametinib (unsolvated) has very low aqueous solubility and animal dosing gave low exposures. Several solvates were investigated and the DMSO solvate was selected because of better animal exposure and acceptable physicochemical properties. The highest strength tablet (2 mg trametinib) contains 0.25 mg of DMSO. Formulation of a solvate is unusual, but DMSO toxicity is low (as a manufacturing solvent, residues of up to 50 mg per day are typically allowed). The label claim is the equivalent amount of unsolvated trametinib.

Trametinib (as DMSO) is still practically insoluble in water, independent of pH (0.2 to 0.3 µg/mL); solubility in simulated intestinal fluids is somewhat higher (but decreases after about an hour, presumably due to formation of solid unsolvated trametinib which is less soluble).

Drug product

The drug products are immediate release tablets for oral administration containing trametinib DMSO equivalent to 0.5 mg, 1 mg or 2 mg of trametinib (non-solvated parent). The tablets are distinguished by colour, shape and markings. Tablets are not scored.

High density polyethylene (HDPE) bottle packs of 7 or 30 tablets, with child-resistant closures (CHC), are proposed. These contain a desiccant.

Clinical trial formulations

Very similar tablet formulations have been used in all clinical trials (with a wider range of strengths used in some Phase I studies). The Phase III study MEK114267 used 0.5, 1.0 and 2.0 mg trametinib tablets. There are minor differences between these Phase III tablets and the tablets proposed for registration (a change in the 0.5 mg colour coat, and a change in tablet diameter/thickness for the 2 mg tablet). No bioequivalence study was conducted but, given the slight changes and dissolution data, these differences should not affect bioavailability.

The dabrafenib/trametinib combination Study BRF113220 used the same 0.5, 1 and 2 mg trametinib tablet formulations as used in Study MEK114267. The dabrafenib capsules used in BRF113220 were mostly gelatine capsules (for Study Parts A, B, and C), which have a lower dabrafenib bioavailability than the registered hydroxypropylmethylcellulose (HPMC) capsules used in Part D.

Biopharmaceutics

The sponsor states that trametinib is a compound with low solubility and high permeability, that is, a Biopharmaceutics Classification System (BCS) Class II drug. Trametinib is lipophilic and the drug is highly bound to plasma proteins but also partitions significantly into red blood cells (although pharmacokinetic (PK) studies only measured plasma concentration).

Trametinib PK is linear. Individual trametinib plasma profiles are conventional, albeit with a long elimination half-life. Trametinib is metabolised by deacetylation, apparently by esterases, followed by secondary metabolism. Excretion is chiefly faecal.

An absorption, distribution, metabolism, excretion study (ADME: MEK113708) was undertaken in just two male subjects with solid tumours, under fasting conditions. This

used a 2 mg oral solution dose of [14C] trametinib DMSO, solubilised as a cyclodextrin complex.

An absolute bioavailability study (MEK115064) was undertaken in four patients with solid tumours. This used a 2 mg oral tablet dose given fasting, with an intravenous (IV) dose of [14C] trametinib (5 µg) given 1.5 hours later (to coincide with the oral T_{max}). The [14C]-radiolabelled trametinib was dissolved in an aqueous solution using a cyclodextrin.

Plasma samples were then analysed for total radioactivity, total trametinib (HPLC-MS/MS) and [14C]-trametinib (HPLC-accelerator mass spectrometry).

Absolute bioavailability was estimated using both AUC_{0-t} (up to last sampling time). The bioavailability of the trametinib 2.0 mg tablet was moderate to high [generalised least aquare (GLS) mean 72.3% (90% confidence interval (CI) 50.0, 104.6)] and individual values ranging from 45.7% to 92.8%. The high absolute bioavailability and low clearance (CL) suggest low hepatic extraction of trametinib in addition to low first-pass metabolism. (The sponsor has argued that cyclodextrin complexation of the IV dose will not affect in-vivo PK.).

Study MEK113709 was a crossover study of the effect of food in 24 patients. Trametinib has an effective elimination half-life of about 4.4 days, so a complete wash-out period is >20 days. The sponsor argued that it was most appropriate to conduct the study in patients with tumours, but that it was then not acceptable to introduce a long washout delay (that is, >14 days) after single study doses before starting active treatment in patients. Furthermore, the known large inter-subject variability after single doses made a parallel design impractical because of the large sample size needed. Thus a two way crossover study with an incomplete wash-out was used with seven days blood sampling. Due to the incomplete wash-out, plasma concentrations after the second dose were corrected for residual concentrations from the first dose.

Table 1: Summary of the results of the mixed effects model to estimate effect of food on GSK1120212 PK parameters

Summary of the Results of the Mixed Effects Model to Estimate Effect of Food on GSK1120212 PK Parameters			
PK Parameter	Geometric Least Squares Mean		Ratio (90% CI)
	2.0 mg/High-fat, High-calorie meal	2.0 mg/Fasted	
corrAUC(0-∞) (ng*hr/mL)	365.90	407.73	0.897 (0.800, 1.007)
corrAUC(0-last) (ng*hr/mL)	195.81	257.83	0.759 (0.697, 0.828)
corrCmax (ng/mL)	2.739	9.111	0.301 (0.243, 0.371)

Abbreviations: corrAUC(0-∞), corrected area under the concentration-time curve from time zero (pre-dose) extrapolated to infinity; corrAUC(0-last), corrected area under the concentration-time curve from time zero (pre-dose) to last observed time; corrCmax, corrected maximum observed concentration; CI, confidence interval

Administration with a high-fat, high-calorie meal resulted in a dramatic (70%) decrease in C_{max} compared to fasting administration. Exposure was also reduced but only slightly (AUC_{0-t} reduced about 25%).

Advisory committee considerations

The application was considered at the 151st meeting of the Pharmaceutical Sub-Committee (PSC) (2013/3). The PSC recommendations were:

1. The PSC endorsed all the questions raised by the TGA in relation to the pharmaceutic and biopharmaceutic aspects of the submission by GlaxoSmithKline Australia Pty Ltd to register Mekinist film coated tablets containing 0.5 mg, 1 mg and 2 mg of trametinib (as DMSO).
2. The PSC:
   - Noted the limitations (for example, number of patients enrolled in the studies, sampling for a relatively short duration that is very close to the half-life of the drug substance, and incomplete wash-out period) in the bioavailability studies provided in support of this submission. The PSC considered that the correction of plasma concentrations was not clear and advised that this may have caused the observed period effect in the food study. The PSC however agreed that while not ideal, given the nature of the drug, its intended use and patient population, the results from the food-effect study are sufficient to provide a meaningful estimate of the impact of a high fat high calorie meal on the kinetics of the drug.
   - Considered the absence of bioavailability studies with the two lower tablet strengths proposed for registration acceptable.
3. In relation to the population pharmacokinetic (PopPK) analysis, the PSC:
   - Noted that although the analysis seemed sound, the model appeared to possibly under-predict C_{max} and C_{min}. The visual predictive checks were however not faceted on covariates, and so are of little utility in model evaluation. Furthermore, although the impact of covariates (for example, sex and weight) on indices of exposure was investigated, this was only for the average patient. The PSC agreed that it would have been far more pertinent to investigate the proportion of patients expected to meet the "target of 10 ng/ml", particularly investigating the covariate subgroups. Even if the model is accepted on face value, there is little justification for the selection of the 2 mg starting dose and the lack of need for dosage adjustment based upon weight and sex. The analysis evaluated the importance of several covariates, all of which were deemed not significant. These were reported in the "Special Patient Populations" section of the PI.
   - Noted that there was no strong relationship between the proportion of responders and measure of exposure, as the number of responders plateaued with trametinib average concentration (C_{avg}) >13 ng/mL. The PSC considered that it would have been helpful to have information on the relationship with a concentration below 10 ng/mL.
   - Advised that the pharmacometric analyses must be formally evaluated by the TGA including obtaining the key model files and datasets electronically from the sponsor and re-running them during the evaluation process to ensure the results are consistent with the sponsor's claims. The PSC considered that this is relevant given that the analyses were used to support dose recommendations and inclusion of material in the PI and thus require formal evaluation.
4. In the Product Information:
   - The formatting should be reviewed and the International System (SI) units should be used.

There is no requirement for this submission to be reviewed again by the PSC before it is presented for consideration by the ACPM.

The PI will be reviewed following ACPM consideration.

Quality summary and conclusions

Registration is recommended with respect to chemistry, quality control and biopharmaceutic aspects.

III. Nonclinical findings

Introduction

The general quality of the submitted nonclinical studies was reasonable. The range of studies was limited but consistent with the International Conference on Harmonisation (ICH) guidelines for anticancer drugs. Pivotal studies examining repeat-dose toxicity, genotoxicity and reproductive toxicity were conducted under Good Laboratory Practice (GLP) conditions with the proposed trametinib form, namely, a DMSO solvate. While the exposure ratios are low in the animal studies, they are adequate to address the clinical relevance of the observed toxicities.

The following studies were not considered relevant to the safety evaluation of trametinib as a monotherapy or as a combination therapy with dabrafenib, and are not included in this report:

1. Primary pharmacology studies which examined the effect of combination treatment of trametinib with drugs other than dabrafenib (UH2008/00044/00; UH2009/00046/00; UH2009/00093/00; UH2010/00044/00; UH2010/00026/00; UH2010/00052/00; UH2010/00051/00; 2010N105273_00; UH2010/00040/00; 2011N113163_01; 20121N134985_00).
2. A 7-day rat toxicity study which examined the effect of combination treatment of trametinib with GSK2126438, a P13K inhibitor (CD2009/00139/00).

Pharmacology

Mechanism of action

Trametinib is an allosteric non-competitive inhibitor of the activation and kinase activity of mitogen-activated extracellular signal regulated kinases, MEK1 and MEK2. MEK1 and MEK2 are part of the mitogen-activated protein kinase (MAPK) signal transduction pathway. After phosphorylation by BRAF kinase, MEK1 and MEK2 phosphorylate ERK1 and ERK2, which translocate to the nucleus and are involved in a number of cellular mechanisms, including regulation of cell growth, proliferation and differentiation.

The MAPK pathway is a proliferation pathway in normal cells and in many human cancers, including melanomas. The pathway can be constitutively activated by alterations in specific proteins, including BRAF, a serine/threonine kinase. Oncogenic mutations in BRAF and RAS signal through the extracellular signal regulated kinases MEK1 and MEK2. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 60% of melanomas. The most common BRAF mutation is V600E which increases BRAF activity by 10- to 450-fold.

In vitro studies

Trametinib

In vitro studies demonstrated the ability of trametinib to block BRAF catalysed MEK1 and 2 activation by binding to unphosphorylated MEK1 and MEK2 (IC50 values of 0.7 and 0.9nM, respectively). Binding was allosteric, blocking phosphorylation on Ser218, and not competitive with adenosine triphosphate (ATP). Trametinib also bound less strongly to phosphorylated MEK1 and MEK2 (IC50 = 13.2 and 10.7 nM, respectively). Trametinib did not inhibit BRAF or CRAF kinase activity and was inactive against 44 other kinases (IC50 >10 μM). There was no difference in activity between DMSO solvate and the free acid form of trametinib.

The activity of trametinib was further examined in a broad range of cancer cell lines, with 80% of BRAF mutant cell lines and 72% of RAS mutant cell lines sensitive compared with 28% of wild type RAS and RAF cell lines (gIC50 = <50 nM). In human melanoma cells A375 BRAFV600E, inhibition of pERK by trametinib was reversed within three hours after wash-out, with a minimum concentration required to induce growth inhibition of 100 nM. In human colorectal carcinoma cells, inhibition of phosphorylation of ERK and MEK occurred within one hour, with cells undergoing apoptosis following G0/G1 arrest. Trametinib inhibited cell proliferation in a range of cancer cell lines, including pancreatic cancer cells, certain haematopoietic cancer cells and breast cancer cells. It also inhibits the proliferation of normal Human Umbilical Vein Endothelial Cells **(**HUVEC) cells, but not non-proliferating HUVEC.

Metabolite M5 had similar MEK inhibition activity to trametinib, but because of its low exposure in humans (<11%) compared to trametinib, it is unlikely to contribute significantly to pharmacological activity. Metabolite M7 has 10-fold less potency than trametinib in relation to inhibition of MEK activity and accounts for <15% of drug related compounds in human plasma and therefore is also unlikely to contribute significantly to pharmacological activity.

Dabrafenib/Trametinib

Combination treatment with dabrafenib and trametinib (10:1 ratio) in A375 BRAFV600E mutant melanoma cell clones resistant to dabrafenib resulted in decreased ERK phosphorylation and increased inhibition of outgrowth of the tumour cells (19-50% compared to the best single agent). In 17 BRAFV600E/K/D mutant melanoma cell lines, combination treatment had a synergistic or additive effect on cell growth inhibition of dabrafenib-sensitive cell lines.

An in vitro study with dabrafenib alone demonstrated the sensitivity of seven melanoma cell lines with BRAF mutations (V600E/K/D) to inhibition by dabrafenib and, to a less extent, its metabolites, M7 and M8. Growth inhibition in these cells correlated with inhibited ERK phosphorylation.

In-vivo studies

Trametinib

Trametinib was tested for its ability to inhibit BRAF or KRAS mutated human tumour xenografts in mice. Trametinib inhibited tumour growth in a dose- and time-dependent manner in human melanoma, lung, pancreatic and colon cancer xenografts, although the results of the various studies are quite variable. With the A375 BRAFV600E human melanoma xenograft, trametinib at 0.3mg/kg/day (equivalent to approximately four times the clinical exposure based on AUC) produced tumour growth inhibition of 82% at Day 22. In a separate study, trametinib at 1 mg/kg/day (equivalent to approximately 18 times the clinical exposure based on AUC) produced tumour growth inhibition of 78% over 14 days. Trametinib also inhibited tumour growth in A549 lung carcinoma xenograft (KRAS

mutant) and in Colo205 colon carcinoma xenograft (BRAFV600E mutant), but to a lesser extent. The efficacy of trametinib monotherapy at clinically relevant exposures was not adequately demonstrated by the available nonclinical studies.

Dabrafenib/Trametinib

Combination treatment in a 10:1 dose ratio (dabrafenib (10-30mg/kg/day) and trametinib (0.1-0.3mg/kg/day) of mice bearing A375 BRAFV600E human melanoma xenograft for 14 or 29 days did not produce an additive anti-tumour effect, compared with single drug treatment groups. Studies of longer duration (56 or 90 days) with combination treatment produced a more pronounced anti-tumour effect, producing a significant increase in tumour growth inhibition, together with increased survival, compared with single drug treatment. Administration of dabrafenib (10mg/kg/day) with trametinib (0.1mg/kg/day) produced 95% tumour growth inhibition (approximately equivalent to the clinical exposure based on AUC). The mouse studies suggested that the dabrafenib/trametinib combination was more effective than either drug alone only with the prolonged treatment schedule. There was no difference between the combination and each drug alone with a treatment regimen of less than one month.

Secondary pharmacodynamics

Trametinib showed no activity in a broad biochemical assay screen of 50 kinases in one study and 171 kinases in a second study (IC_{50} >10 μM). Trametinib at 10 μM also had no inhibitory effect against the following enzymes: phospholipase A2, cyclooxygenase isoform 1 (COX1), constitutive NO synthesis (NOS), phosphodiesterase 4, protein kinase C, acetylcholinesterase, monoamine oxidase A.

Safety pharmacology

In in vitro studies, trametinib inhibited hERG ion channel current in a preliminary assay in Chinese hamster ovary cells and in a definitive assay in human embryonic kidney cells at an IC50 of 3.7 μM (2277 ng/mL) and 1.54 μM (948 ng/mL), respectively (>1000 times the steady state unbound plasma concentration). In a rabbit heart ventricular wedge preparation, trametinib had no effect on QT interval[6] at doses up to 30 μM (18450 ng/mL) (>10000 times the steady state unbound plasma concentration), but did significantly decrease the isometric contractile force (ICF) (-64%) and the Tp-e interval (-25%) at 30 μM (less effect on ICF at 10 μM, -16%), which were far above the clinical C_{max} (36 nM). The mechanisms of decreased ICF and Tp-e interval without effects on QT or QRS are unknown. The study author suggested that the effects could be associated with a potential inhibitory effect on the inward calcium current and possibly effects on the fast sodium current. Taken together with the high plasma protein binding of trametinib, the data indicates that these cardiovascular effects are not clinically relevant.

In in-vivo studies in dogs, there were no treatment-related effects on electrocardiography parameters (blood pressure (BP), heart rate, electrocardiogram (ECG) intervals and ECG waveforms) or on body temperature after a single IV infusion of 1 mg/kg or after an oral dose (maximum tolerated) of 0.075 mg/kg (C_{max} of the in vitro study 68 times the clinical C_{max} and C_{max} of the oral study below the clinical C_{max}).

In clinical trials, cardiac toxicity in the form of decreased left ventricular ejection fraction (LVEF) has been observed with MEK1/MEK2 inhibitors and is described as a common adverse effect in cancer patients taking trametinib. Few significant QTc or ECG effects have been observed in clinical trials. Cardiac toxicity was not observed in chronic studies in rats and dogs, and effects on the myocardium (myocardial necrosis) were only observed at high, non-tolerated dose levels (≥1 mg/kg/day, similar to the clinical exposure based on

[6] In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle

AUC) in dose range-finding studies in rats. Investigative studies to examine possible mechanisms for LVEF were conducted in vitro in cardiomyocytes and in-vivo in mice (because of the ability of mice to tolerate higher systemic exposure) at up to 0.5 mg/kg/day for three weeks. The in vitro studies established that the mechanism is not related to cell viability or impaired mitochondrial function. The in-vivo study reported a decrease in left ventricular functional parameters at 0.5 mg/kg/day (equivalent to seven times the clinical exposure based on AUC). The data suggests humans have a higher sensitivity than animals to trametinib-related decreased LVEF, but not to other forms of cardiac toxicity. Cardiac effects are potential toxicity in patients.

Examination of general behaviour in rats over 24 hours showed reduced spontaneous locomotion and reduced body weight (BW) gain together with poor clinical conditions at 100 mg/kg (approximately 25 times the clinical C_{max}). Examination of respiratory function in rats showed no effects on ventilatory function or on airway resistance over five hours, but there was a transitory, small decrease in body temperature (-0.8°C compared to vehicle control) at 0.125 mg/kg (approximately 0.2 times the clinical C_{max}) which may be clinically relevant.

Pharmacodynamic drug interactions

The potential synergistic effects of dabrafenib/ trametinib combination treatment are discussed above.

Pharmacokinetics

Absorption: Nonclinical PK studies were conducted in the mouse, rat, dog and monkey. Absorption following single dose administration of trametinib was variable and depended on solubility and dissolution in the formulation, but was similar in all species. A micronised version of the DMSO solvate was selected for development. The bioavailability varied across species with absolute bioavailability of 111%, 48% and 86% for the acetic acid solvate form in mouse, rat and dog, and 42% and 49% for the DMSO solvate in rat and monkey, respectively. The volume of distribution was high in all species (including humans) indicating wide tissue distribution. The terminal half-life (T½) ranged from 3.7 hours in mouse, 6 hours in rat to 14.5 hours in dogs, which were shorter than in humans ~5 days).

In repeat dose studies with trametinib in mice, rats and dogs, exposure (based on AUC and C_{max}) was similar in males and females (though higher exposures were observed in females than in males in the three-week repeat dose study in rats) and increased more than dose-proportionally until steady-state was reached, which was approximately Day 7 in mice and Week 4 in rats and dogs. There was no evidence of accumulation after steady-state levels were reached.

In a repeat dose combination study with dabrafenib/trametinib in dogs, dabrafenib exposure increased less than dose-proportionally with no accumulation over four weeks, while trametinib exposure increased dose-proportionally. The toxicokinetics for trametinib and for dabrafenib and its metabolites were similar to that seen with each drug individually indicating a lack of PK interactions between the two drug substances.

Distribution: Trametinib was highly bound to plasma protein in all species, including humans (96-98% in mouse, rat, dog, monkey and human plasma). Blood cell association in human blood IV was concentration-dependent, with higher partitioning to blood at lower concentrations (~85% at 1-10 ng/mL) and equal partitioning at higher concentrations (49% at 50 ng/mL). There was no difference between the blood of healthy and cancer-bearing individuals. Tissue distribution in rats following 14C-trametinib administration was widespread, with very high levels in liver, low levels in brain and no evidence of

selective binding to melanin-containing tissues. Radioactivity was declining in all tissues by 24 hours and was below the limit of quantification in most tissues by 168 hours.

Metabolism: Metabolism of trametinib in rats, dogs and humans was through deacetylation alone or in combination with oxidation, followed by N- or O-glucuronidation. in vitro studies with microsomes indicate low intrinsic CL in mice, rats, dogs and humans, and high CL in monkeys. In human hepatocytes, metabolites detected were a deacetylation product (M5), the glucuronidation product of M5 (M6), and a deacetylation and oxidation product (M7). All human metabolites were detected in one or more animal species. Deacetylation is the major pathway of elimination and is likely to be mediated by hydrolytic esterases. The use of selective inhibitors suggested the involvement of CYP3A4 in the metabolism of trametinib. In the presence of human microsomes, trametinib inhibited CYP2C8, 2C9, and 2C19, while activation/induction was observed in the CYP3A4 (midazolam) assay. This is consistent with the moderate induction of human pregnane X (for which CYP3A4 is a target) in HepG2 cells in vitro.

In in-vivo studies in rat and dog, unchanged trametinib was the major component in plasma. In rats, the major metabolites were products of mono-oxidation (M12), deacetylation (M5), a combination of both (M7) and N-demethylation (M13). Excretion was largely unchanged trametinib in the faeces, with the absorbed fraction metabolised to glucuronide conjugates of mono-oxidation and deacetylation and excreted via the bile. In the dog, metabolites were products of deiodination (M10), oxidation (M7& M12) and deacetylation (M5). Excretion was mainly via faeces (9-12% unchanged trametinib).

Excretion: The major excretion route in all species was the faeces. In rats, based on urinary and biliary recoveries, absorption was estimated to be at least 41.3% of the oral dose. In dogs, based on urinary excretion and faecal metabolites, absorption was at least 28-35% of the oral dose.

Conclusion: On the basis of the submitted data, the PK of trametinib in animal species is similar to the PK in humans, with moderately rapid absorption, high plasma protein binding, metabolism involving deacetylation and oxidation to common metabolites, and elimination via the bile and faeces. In combination studies with dabrafenib, there was no evidence that either drug affected the kinetics of the other in dogs.

Pharmacokinetic drug interactions

The potential for other drugs to affect the PK of trametinib is considered low since it is mainly deacetylated via hydrolytic esterases, with CYP3A4 having a secondary role. Trametinib is also not a substrate for human P-glycoprotein (P-gp) or breast cancer resistant protein (BCRP) and inhibition of these transport systems is not likely to increase trametinib concentrations. Co-administration with dabrafenib, a CYP3A4 inducer, in animal studies did not alter trametinib exposure.

The potential for trametinib to affect the PK of other drugs is considered to be low. In in vitro studies, trametinib was an inhibitor of CYP2C8, CYP2C9 and CYP2C19, and an inducer of CYP3A4. The most potent inhibition was for CYP2C8 (IC50 = 0.34 μM, equivalent to nine times the clinical bound C_{max}). Induction of CYP3A4 had an EC50 of 1.7 μM, equivalent to 40 times the clinical bound C_{max}. Trametinib inhibited OATP1B1, OATP1B3, P-gp and BCRP, with IC50 values 1.3, 0.94, 5.5 and1.1 μM, respectively, compared to the clinical C_{max} of 36 nM. The unbound plasma concentration of trametinib (unbound fraction 0.03) would be insufficient to affect the PK of other drugs. Co-administration of trametinib with dabrafenib, a CYP2C8 and CYP3A4 substrate, in animal studies (and in clinical studies) did not affect dabrafenib exposure.

Toxicology

Single-dose toxicity

Oral dose-range finding studies were conducted with trametinib in rat and dog using single dose exposure. In rats, there was decreased BW at ≥ 3mg/kg/day accompanied by lesions in the liver at ≥ 10mg/kg/day. The maximum non-lethal dose was 100 mg/kg/day (equivalent to 33 times the clinical AUC). In dogs, trametinib at 3 mg/kg was not tolerated and dogs were killed in a moribund condition, with decreased BW, decreased reticulocytes, increased WBC and pathological evidence of gastrointestinal (GI) damage, lymphoid depletion and reduced bone marrow cellularity. The maximum non-lethal dose was 0.5 mg/kg/day (equivalent to six times the clinical AUC). Based on these studies, trametinib has a low order of acute toxicity by the clinical (oral) route.

Repeat-dose toxicity

Trametinib

Repeat-dose studies with trametinib up to 13 weeks were conducted in rats and dogs, consistent with ICH S9 guidelines. All studies with trametinib were conducted by the oral route with once daily dosing. The early studies in rat (up to 14 days) were conducted with the acetic acid solvate, and all other studies in rat and dog were conducted with the DMSO solvate.

Relative exposure for trametinib monotherapy

Exposure ratios for trametinib have been calculated based on animal/human AUC_0-τ (mean of males and females unless noted otherwise). Human reference values are from Clinical Study MEK111054.

Table 2: Relative exposure to trametinib in repeat-dose toxicity studies

Species	Study duration	Dose (mg/kg/day)	AUC_{0-24h} (ng·h/mL)	Exposure ratio#
Rat (SD)	14 days	0.1	72.5	0.20
		0.3	100	0.27
		1	344	0.93
	3 weeks	0.016	35.0/60.2	0.09/0.17
		0.031	64.2/126	0.17/0.34
		0.0625	129/211	0.35/0.57
		0.125	218/460	0.59/1.2
	13 weeks	0.031/0.016[a]	95.4/102	0.26/0.28
		0.0625/0.031[a]	277/158	0.75/0.43
		0.125/0.0625[a]	ND	-
Dog (Beagle)	3 weeks	0.025/0.015[a]	159/120	0.43/0.32
		0.038/0.020[a]	282/211	0.76/0.57
		0.075/0.025[a]	ND/205	-/0.55
	13 weeks	0.0075	48.7	0.13
		0.015	101.2	0.27
		0.030→0.023[b]	139[c]	0.38
Human*	Day 15	2 mg/day	370	–

animal/human AUC ratio; * subjects with solid tumours or lymphomas; ND = no data (dosing was discontinued before scheduled sacrifice); a, male/female; b, Due to poor tolerability at 0.03 mg/kg/day, dosing was stopped on day 11/12 and resumed at 0.023 mg/kg/day on day 21/22; c, AUC at 0.023 mg/kg/day in week 13.

Major toxicities

The nonclinical toxicity associated with trametinib included morbidity related to skin lesions and GI effects, and haematopoietic abnormalities. Other adverse effects were observed in bone, kidney, liver, heart, adrenal, ovaries and lymphoid tissues. Low animal:human exposure ratios and the lack of clear NOAELs (no observed adverse effect levels) in some studies raise the potential clinical relevance of these toxicities.

Skin lesions, including acanthosis, ulceration and crust formation, were common in rats and occurred early and persisted throughout treatment. The changes observed were dose-related, but demonstrated reversibility during the recovery period. Female rats were more sensitive with effects occurring at ≥0.031 mg/kg/day (equivalent to 0.4 times the clinical exposure based on AUC). In dogs, skin lesions were less common and were observed only in the three month study at the highest dose, 0.03 mg/kg/day (no AUC data), which was not tolerated by the animals and necessitated a dose reduction. No skin lesions were observed at 0.023 mg/kg/day for three months (equivalent to 0.4 times the clinical exposure based on AUC) or 0.038 mg/kg/day for three weeks (approximately 0.8 times the clinical exposure). In clinical studies with trametinib and other MEK inhibitors, skin rash is the most common adverse effect and considered related to the pharmacological activity of trametinib. The skin lesions are considered to be clinically relevant.

GI effects were observed in both rats and dogs, but were more commonly associated with morbidity in dogs. In rats, there was erosion, ulceration, hyperplasia of mucosal epithelium of the gastrointestinal tract (GIT) at high doses, > 1 mg/kg/day (similar to clinical exposure based on AUC) and inflammation, and/or erosion of the glandular mucosa of the stomach at ≥0.031 mg/kg/day (equivalent to 0.3 times the clinical exposure based on AUC). In dogs, there was reduced food intake, abnormal faecal discoloration, and emesis at dose levels above 0.025 mg/kg/day (equivalent to 0.4 times the clinical exposure based on AUC). Macroscopic lesions of red discoloration were seen in unscheduled kills at >0.038 mg/kg/day (0.8 times the clinical exposure). In clinical studies, diarrhoea, nausea, vomiting and constipation were commonly observed and considered likely to be related to the pharmacological activity of trametinib. The GI effects are considered to be clinically relevant.

Haematopoietic effects observed at the lower dose levels in rats and dogs were generally consistent with an inflammatory response to skin lesions in rats and to GI effects in dogs, and included increases in WBC and neutrophils. In rats after 13 weeks, there was also haematopoietic cell necrosis at 0.0625 mg/kg/day (equivalent to 0.7 times the clinical exposure based on AUC). At high, non-tolerated doses, trametinib treatment was associated with reduced reticulocytes, RBC, platelets and lymphocytes, thymus and lymphoid atrophy or necrosis, haematopoietic cell necrosis, and hypocellularity of the bone marrow in both species. In clinical studies, mild anaemia was commonly observed. The haematopoietic effects are considered clinically relevant.

Adverse effects on bones (hypertrophy of the epiphyseal growth plate) were observed in rats at ≥0.1 mg/kg/day (equivalent to 0.2 times the clinical exposure based on AUC). Related effects were altered phosphate and calcium homeostasis, evidenced by mineralisation in the stomach, kidney, heart, lung and liver in rats at >0.016 mg/kg/day (equivalent to 0.2 times the clinical exposure based on AUC) and other tissues at higher doses. Specific investigative studies indicated that this effect was secondary to increased serum phosphorus and likely to be related to MEK1 and MEK2 inhibition. Increased serum phosphorus without soft tissue mineralisation was observed in dogs. Similar findings (plus increased serum 1,25-dihydroxyvitamin D3 and FGF-23, a bone derived growth factor, and decreased serum PTH levels) were reported in rats treated with MEK inhibitors,

PD325901 or GEN-A (Diaz et al. 2012[7]) and in mice treated with PD325901 (Ranch et al. 2011[8]). The study by Diaz and co-authors suggested that MEK inhibitors upregulate 25-hydroxyvitamin D3 1-alpha-hydroxylase (Cyp27b1), a rate-limiting enzyme in vitamin D activation and downregulate 1,25-dihydroxyvitamin D3 24-hydroxylase (Cyp24ab1), which degrades active vitamin D. The authors proposed that the dysregulation of phosphate and calcium homeostasis by MEK inhibitors involve blockage of FGF-23 signalling in the kidney. As suggested by the sponsor in the Nonclinical Overview, increased serum phosphorus and soft tissue mineralisation are probably associated with inhibition of MEK-dependent FGF signalling. Similar effects were observed in rats treated with a FGF receptor tyrosine kinase inhibitor (Brown et al. 2005[9]). Clinical studies did not report any changes to serum phosphorus, suggesting rats and dogs may be more sensitive to this effect.

Renal cortical injury (tubular degeneration, vacuolation and regeneration) was observed in rats at >1 mg/kg/day and tubular mineralisation at >0.1 mg/kg/day. Tubular necrosis was evident at lethal doses. Serum albumin levels tended to be decreased in both rats and dogs and the decrease might be related to the renal and/or hepatic (see below) abnormalities.

Effects on the liver included necrosis at high, non-tolerated dose levels and increased vacuolation in rats at ≥0.016 mg/kg/day (equivalent to 0.1 times the clinical exposure based on AUC). These effects were accompanied by changes in liver enzymes (AST, ALT), which were reversible. Hepatic toxicity was also a feature of another MEK inhibitor, PD325901.

Ocular effects have not been observed in nonclinical studies in rats or dogs; however, in clinical studies, visual disturbance (mainly central serous retinopathy) has been reported in patients taking trametinib. From the current literature, it is unclear whether this effect is related to MEK inhibition, but ocular abnormalities appear to be class effects of MEK inhibitors (Akinleye et al 2013[10]; Renouf et al 2012[11]).

Myocardial necrosis in rats at lethal doses in dose range-finding studies and is discussed above under Safety Pharmacology. Other organs affected are adrenal (cortical/hypertrophy/ hyperplasia in rats at >0.0625 mg/kg/day and in dogs at >0.25 mg/kg/day), ovaries (multiple cyst follicles and decreased number of corpora lutea in rats at >0.016 mg/kg/day), mammary gland (necrosis of acinar epithelium in rats at >1 mg/kg/day).

Dabrafenib/Trametinib

A four-week repeat-dose oral study with dabrafenib/ trametinib combination was conducted in dogs with once daily dosing for trametinib and twice daily dosing for dabrafenib, which corresponds to the proposed clinical dosing frequency.

Relative exposure for trametinib and dabrafenib combination therapy

Exposure ratios for trametinib and dabrafenib have been calculated based on animal/human $AUC_{0\text{-}24h}$ (mean of males and females). Human reference values are from Clinical Study BRF113220.

[7] Diaz D et al. 2012, Phosphorus dysregulation induced by MEK small molecule inhibitors in the rat involves blockade of FGF-23 signalling in the kidney. Toxicological Sciences, 125: 187-195.
[8] Ranch D et al. 2011, Fibroblast growth factor 23 regulates renal 1,25-dihydroxyvitamin D and phosphate metabolism via the MAP kinase signaling pathway in *Hyp* mice. Journal of Bone and Mineral Research, 26: 1883–1890.
[9] Brown AP et al. 2005, Cartilage dysplasia and tissue mineralisation in the rat following administration of a FGF receptor tyrosine kinase inhibitor. Toxicologic Pathology, 33: 449-455.
[10] Akinleye A et al. 2013. MEK and the inhibitors: from bench to bedside. Journal of Hematology & Oncology, 6:27 (http://www.jhoonline.org/content/6/1/27).
[11] Renouf DJ et al. 2012. Ocular toxicity of targeted therapies. Journal of Clinical Oncology. 30: 3277-3285.

Table 3: Relative exposure to trametinib and dabrafenib in repeat dose study

Species	Study duration	Dose (mg/kg/day)	AUC_{0-24h} (ng·h/mL)*	Exposure ratio#
Dog (Beagle)	4 weeks	**Trametinib**		
		0.0075	66.7	0.19
		0.0225	202	0.58
		Dabrafenib##		
		5	27100	2.3
		20	82000	7
Human**	Day 21	2 mg trametinib once daily 150mg dabrafenib BID	356/11772	–

* Average of male and female values; # = animal:human plasma AUC0-24h ** subjects with BRAF600 mutant solid tumours; ##Estimated mean AUC0-24h values for dabrafenib are based on actual geometric mean AUC0-12h value of 5886ng.h/mL.

Combination dabrafenib/trametinib treatment in dogs over four weeks produced adverse effects consistent with treatments with either drug alone at these dose levels. Adverse effects in the testes (germinal epithelium degeneration), stomach (granulomatous inflammation), mesenteric lymph nodes (foreign material deposits) and thymus (lymphoid depletion) were noted at >0.0075 mg/kg/day trametinib/5mg/kg/day dabrafenib (equivalent to 0.2/5 times the clinical exposure to dabrafenib/trametinib). One high dose male which was killed on Day 11 due to poor condition showed mild neutrophilic inflammation of the colonic and rectal mucosa and degeneration/necrosis of an extramural right coronary artery with transmural and perivascular neutrophilic and histiocytic inflammation and haemorrhage. Arterial degeneration in the right atrium and papillary muscle of the heart and hypertrophy and haemorrhage of atrioventricular valve of the heart was seen in dogs dosed with dabrafenib alone.

The dog study showed no new toxicity from the combination compared to each drug alone. Co-administration of dabrafenib/ trametinib appeared to alleviate the proliferative effects of dabrafenib on skin. Toxicity profile of the combination was not studied in a second species. A study with BRAF and MEK inhibitors, GSK2366297 and GSK2091976, respectively, in rats showed that the combination alleviated the BRAF inhibitor-induced epithelial hyperplasia/hyperkeratosis in skin and forestomach. However, it is noted that proliferative skin lesions were reported in patients treated with the dabrafenib/trametinib combination. The study findings in dogs dosed with BRAF and MEK inhibitors do not appear to predict skin effects of the dabrafenib/trametinib combination in humans.

Genotoxicity

The genotoxic potential of trametinib was adequately examined in in vitro studies in bacteria and mammalian cells and in an in-vivo study in rats. In *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, and in *E. coli* WP2 uvrA, there was no evidence of an increased frequency of mutations. In mouse lymphoma cells, there was no evidence of an increased frequency of mutations at the TK locus. In the rat micronucleus test, there was no increase in the incidence of micronucleated polychromatic erythrocytes at 2 mg/kg/day for two days by mouth (PO). The overall conclusion is that trametinib does not have genotoxicity potential.

Carcinogenicity

Carcinogenicity studies were not conducted. This is in accordance with ICH S9 guidelines as trametinib is intended to treat patients with advanced cancer.

Reproductive toxicity

Very limited assessment of reproductive toxicity was performed with trametinib. This is consistent with ICH S9 guidelines as trametinib is intended to treat patients with advanced cancer. There were no studies on placental transfer or an examination of the potential for excretion of trametinib into milk.

There were no specific fertility studies conducted with trametinib, which is in accordance with ICH S9 guidelines; however, relevant information is available from rat and dog toxicity studies. In males, there was no treatment-related effect on stages of spermatogenesis in rats up to 0.125 mg/kg/day (equivalent to 0.6 times and approximately similar to the clinical exposure, based on AUC) or in dogs up to 0.075 mg/kg/day. In female rats, there was an increase in ovarian cystic follicles and a decrease in corpora lutea at ≥0.016 mg/kg/day (equivalent to 0.3 times the clinical exposure based on AUC). While this effect is reversible, it is consistent with literature reports for a role for MEK1/MEK2 in folliculogenesis (Shiota,et al. 2003[12]; Kihara, et al. 2006[13]; Sriraman, et al. 2008[14]) and is likely to be related to the pharmacological effect of trametinib. It is considered to indicate a potential for trametinib to affect female fertility.

Testicular germinal cell degeneration was observed in dogs treated with the dabrafenib/ trametinib combination, consistent with findings in dogs treated with dabrafenib. Testicular toxicity of dabrafenib was not affected by combination with trametinib. Testicular toxicity is a potential toxicity in patients taking the combination.

Table 4: Relative exposure

Species	Study	Dose* (mg/kg/day)	AUC_{0-24h} (ng·h/mL)	Exposure ratio#
Rat (SD)	Embryofoetal development	0.062/0.016	52.3†	0.14
		0.094/0.031	110†	0.30
		0.125/0.062	149†	0.40
Rabbit (Dutch-belted)	Embryofoetal development	0.077/0.0385	31.9‡	0.09
		0.154/0.077	56.4‡	0.15
		0.308/0.154	127‡	0.34
Human**		2 mg once daily	370	–

* Loading dose on GD 6 (rat) or 7 (rabbit)/maintenance dose from GD 7 to 17 (rat) or GD 8 to 19 (rabbit); † AUC after the loading dose on GD 6 (no AUC values after the maintenance); ‡ AUC on GD 11; # = animal:human plasma AUC0–24 h. . ** Subjects with BRAF600 mutant solid tumours; GD = gestation day.

Literature reports in transgenic mice indicate a potential for disruption of MEK1 or ERK2 to produce embryolethality due to defects in placentogenesis (Giroux et al. 1999[15]; Bissonauth, et al. 2006[16]). Mouse Map2k1-/- (MEK1-/-) embryos died at mid-gestation, associated with hypovascularisation of the placenta, decreased labyrinth cell proliferation and increased apoptosis, and abnormal localisation of syncytiotrophoblasts.

[12] Shiota M, Sugai N, Tamura M, Yamaguchi R, Fukushima N, Miyano T, Miyazaki H. 2003. Correlation of mitogen-activated protein kinase activities with cell survival and apoptosis in porcine granulosa cells. Zoolog Sci. 20(2):193-201

[13] Kihara S, Yamamoto H, Ohba T, Shimasaki S, Okamura H. 2006. Activation of follistatin promoter by GnRH in LbetaT2 gonadotroph cells. Endocr J. 53(2):225-35

[14] Sriraman V, Modi SR, Bodenburg Y, Denner LA, Urban RJ. 2008. Identification of ERK and JNK as signaling mediators on protein kinase C activation in cultured granulosa cells. Mol Cell Endocrinol. 294(1-2):52-60.

[15] Giroux S, Tremblay M, Bernard D, Cardin-Girard JF, Aubry S, Larouche L, Rousseau S, Huot J, Landry J, Jeannotte L, Charron J. 1999. Embryonic death of Mek1-deficient mice reveals a role for this kinase in angiogenesis in the labyrinthine region of the placenta. Curr Biol, 9:369-372.

[16] Bissonauth V, Roy S, Gravel M, Guillemette S, Charron J. 2006. Requirement for Map2k1 (Mek1) in extra-embryonic ectoderm during placentogenesis. Development, 133:3429-3440.

The embryofoetal development study in rats showed only minor maternal effects (decreased BW gain) and foetal toxicity (low foetal weights), with no evidence of teratogenicity. Foetal effects were observed at 0.094/0.031 mg/kg/day (loading/maintenance doses; equivalent to 0.3 times the clinical exposure). Higher doses (0.375/ 0.125 mg/kg/day, equivalent to 1.8 times the clinical exposure based on AUC) in a small number of pregnant rats resulted in an increase in post-implantation loss.

The embryofoetal developmental study in rabbits reported evidence of maternal and foetal toxicity together with an increase in skeletal defects at all dose levels (>0.077/0.0385 mg/kg/day, equivalent to 0.1 times the clinical exposure based on AUC). Foetal abnormalities included enlarged fonticulus of the skull and curved scapular spine at the high dose 0.308/0.154 mg/kg/day (0.3 times the clinical exposure), and incomplete ossification of skull bones and sternebrae at all doses. On the basis of the above information, trametinib should be considered to have potential to affect female fertility and embryofoetal development.

There are no embryofoetal development studies with the dabrafenib/trametinib combination. This is acceptable as there is evidence of embryofoetal toxicity in animal studies for both agents.

Pregnancy classification

The sponsor has proposed Pregnancy Category D. The sponsor recommends that trametinib should not be administered to pregnant women or nursing mothers, and also recommends that women of childbearing age should use effective methods of contraception.

The nonclinical data and literature reports indicate that treatment with trametinib at the proposed levels of exposure during pregnancy has the potential to lead to foetal toxicity. Pregnancy Category D is appropriate.

Local tolerance

The in vitro studies conducted did not demonstrate a potential for trametinib to be an eye or skin irritant; however, the IV local lymph node assay in mice gave a positive result for skin sensitisation. This is in contrast to the literature reports that indicate inhibition of MEK1/MEK2 lead to indirect inhibition of hypersensitivity (Uchi, et al. 2003[17]; Muramoto, et al. 2010[18]).

Paediatric use

Trametinib is not proposed for paediatric use at this stage; however, a tolerability and dose-ranging study was conducted in neonate rats. In this preliminary study, trametinib produced mortality, BW loss, and reduced BW gain at dose levels ≥0.05 mg/kg/day. Younger rats were more sensitive to trametinib-induced toxicity. The sponsor is conducting further studies on juvenile animals.

The combination of dabrafenib/ trametinib is not proposed for paediatric use at this stage; however, a juvenile toxicity study with dabrafenib was conducted in neonate rats. Treatment-related effects relating to development were the early onset of sexual maturation in females and shortening of femur/tibia lengths in males and females. Testicular toxicity was evident and correlates with similar effects observed in adult

[17] Uchi H, Koga T, Urabe K, Moroi Y, Furue M. 2003. CX-659S, a Diaminouracil Derivative, Indirectly Inhibits the Function of Langerhans Cells by Blocking the MEK1/2– Erk1/2 Pathway in Keratinocytes. J Invest Dermatol. 120(6):983-9.

[18] Muramoto K, Goto M, Inoue Y, Ishii N, Chiba K, Kuboi Y, Omae T, Wang YJ, Gusovsky F, Shirota H. 2010. E6201, a novel kinase inhibitor of mitogen-activated protein kinase/extracellular signal-regulated kinase kinase-1 and mitogen-activated protein kinase/extracellular signal-regulated kinase kinase kinase-1: in-vivo effects on cutaneous inflammatory responses by topical administration. J Pharmacol Exp Ther. 335(1):23-31.

animals. Renal toxicity related to unidentified deposits was related particularly to pre-weaning treatment and has not been previously observed with dabrafenib in older animals. There were also effects on the non-glandular stomach (epithelial hyperplasia/hyperkeratosis) and thymus (decreased organ weights and increased apoptosis). A NOAEL was not established due to non-reversible renal toxicity at all dose levels.

Nonclinical summary and conclusions

- GlaxoSmithKline Australia Pty Ltd has applied to register trametinib DMSO (Mekinist®) for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic (Stage IV) melanomas. It is proposed to be used as a monotherapy or in combination with dabrafenib mesilate. The proposed dose is 2 mg orally once daily as a monotherapy or in combination with dabrafenib mesilate.
- The data provided in Module 4 were adequate to analyse and assess the nonclinical pharmacological, PK and toxicological properties of trametinib in relation to its proposed clinical use. The data were in general accordance with the ICH guideline on nonclinical evaluation of anticancer pharmaceuticals (ICH S9). The pivotal studies were GLP compliant and conducted with the DMSO solvate, which is the clinical form. While the exposure ratios are low in the animal studies, they are adequate to address the clinical relevance of the observed toxicities.
- The primary pharmacology studies confirmed the activity of trametinib as an allosteric non-competitive inhibitor of the activation and kinase activity of mitogen-activated extracellular signal regulated kinases, MEK1/MEK2. In vitro studies demonstrated the inhibition of MEK1 and MEK2 and that a high percentage of BRAF mutant cancer cell lines were trametinib-sensitive. The deacetylated metabolite (M5) was also active but its low levels in plasma were unlikely to contribute to the pharmacological activity. Combination treatment with dabrafenib/trametinib increased inhibition of A375 BRAFV600E mutant melanoma cells by 19-50% compared with single drug treatment.
- In in-vivo studies with BRAF mutated human tumour xenografts and other human tumour xenografts in mice, trametinib produced tumour growth inhibition only at exposures in excess of the clinical exposure (approximately four-fold). The efficacy of trametinib monotherapy at clinically relevant doses was not adequately demonstrated in nonclinical studies. Combination therapy with dabrafenib in mice carrying the A375 BRAFV600E tumour xenograft produced 95% growth inhibition and increased survival particularly after a longer treatment period (56 or 90 days) at exposures equivalent to the clinical exposure.
- Trametinib showed no activity in a broad biochemical assay screen of kinases or against a range of other enzymes. The safety pharmacology studies examined potential central nervous system (CNS), respiratory and cardiovascular effects. In in vitro studies, the inhibitory effects of trametinib on hERG K+ channel were at concentrations far exceeding clinically relevant exposures. There were no treatment-related effects on QT interval, and the significant decrease in ICF was at concentrations far exceeding clinically relevant exposures. There were no treatment-related effects on electrocardiography parameters (BP, heart rate, ECG intervals or waveforms) in in-vivo studies at twice the clinical C_{max}.

  Clinical studies identified cardiac toxicity in the form of decreased LVEF. Mouse studies reported a decrease in left ventricular functional parameter only at doses well in excess of the clinical exposure. While decreased LVEF is considered to be related to MEK1/MEK2 inhibition, humans may be more sensitive to this effect than animals and ongoing monitoring is required.

There were no treatment-related effects on the CNS that affect general behaviour at dose levels well in excess of the clinical exposure. There was no treatment-related effect on respiratory function, but a transitory, small decrease in body temperature at exposures below the clinical C_{max} may be clinically relevant.

- The PK studies indicate that absorption of trametinib depended on solubility and dissolution in the formulation, but was similar across species. The volume of distribution was high, indicating wide tissue distribution. Plasma protein binding was high for all species (96-98%). In repeat-dose studies, exposure was more than dose proportional until steady-state was reached and T½ was long in all species, including humans. There was no evidence of accumulation. Combination treatment with dabrafenib in animals did not reveal any effect on the exposure of either drug. Trametinib was highly bound to plasma protein in both animals and humans. There was no evidence of prolonged tissue retention. The major pathways of metabolism were deacetylation alone or in combination with oxidation followed by N- or O-glucuronidation. The major enzymes responsible are hydrolytic esterases and CYP3A4, with the latter playing a minor role. The major plasma component was unchanged trametinib. There are no human-specific metabolites. In all species, the major excretion route is the faeces, with metabolites excreted via the bile.
- Potential for other drugs to affect the PK of trametinib is low since it is mainly deacetylated via hydrolytic esterases. Potential for trametinib to affect the metabolism of other drugs is also low since any inhibition of CYP450s, as well as inhibition of transporters, in in vitro assays is well in excess of the clinical exposure.
- In repeat dose studies, there was evidence of increased morbidity associated with skin lesions (acanthosis, ulceration and crust formation) and GI lesions (erosion, inflammation and abnormal faeces), with leukocytosis and neutrophilia. These effects are related to the pharmacological activity of trametinib, occur at lower than clinical exposure levels. Other effects related to the pharmacological effects of trametinib are on bones (hypertrophy of the epiphyseal plate) and on phosphate homeostasis (mineralisation in various soft tissues and renal cortex degeneration). Haematopoietic system was also affected at non-tolerated doses, manifested as haematopoietic cell necrosis, hypocellularity of bone marrow, reduced blood reticulocyte, RBC, platelet and lymphocyte counts, and lymphoid atrophy or necrosis. Other findings were hepatic vacuolation and necrosis (and increased serum transaminase levels), renal tubular degeneration and necrosis, myocardial necrosis, adrenal cortical hypertrophy/hyperplasia, and acinar epithelium necrosis of mammary gland at high, non-tolerated doses in rats, and decreased serum albumin levels at most dose levels in rats and dogs. Increased ovarian cyst follicles and decreased number of corpora lutea were also evident in rats. All of these effects occurred at or below the clinical exposure and are considered clinically relevant. Ocular effects were not observed in animal studies, although visual disturbance has been reported in clinical studies. Combination treatment with dabrafenib produced adverse effects consistent with treatment with either drug alone.
- The genotoxicity data was adequate and produced negative results in in vitro and in-vivo studies. No carcinogenicity studies were performed, consistent with the ICH guidelines for an anti-cancer drug.
- The limited reproductive toxicity studies are consistent with ICH guidelines for an anti-cancer drug. There were no studies on placental transfer or examination of potential transfer of trametinib into milk. There were no specific fertility studies conducted with trametinib; however, there was no evidence of an effect on spermatogenesis stages in male rats, but an increase in cystic follicles and decrease in corpora lutea in female rats at less than clinical exposure indicates a potential for trametinib to affect female fertility. Trametinib also produced evidence of foetal

toxicity and developmental toxicity at exposures below the clinical exposure. The sponsor has proposed Pregnancy Category D, which is considered appropriate.

- Trametinib or a combination with dabrafenib is not proposed for paediatric use at this stage. A juvenile toxicity study with dabrafenib was submitted. Renal toxicity not previously seen in adult studies was identified.

Conclusions

Trametinib monotherapy

- There were no major deficiencies in the nonclinical data on trametinib.
- The primary pharmacology data confirm the activity of trametinib as an inhibitor of the activation and kinase activity of MEK1 and MEK2, and the in vitro sensitivity of a range of cancer cell lines to trametinib treatment. In in-vivo studies, the efficacy of trametinib treatment at clinically relevant doses was not adequately demonstrated.
- The safety pharmacology data on trametinib did not demonstrate any potentially adverse CNS, cardiovascular or respiratory effects at clinically relevant exposures. Myocardial necrosis occurred in rats only at high, non-tolerated doses. Humans may be more sensitive than animals to a particular cardiac toxicity (decreased LVEF) observed in clinical studies.
- The repeat dose studies on trametinib indicate a potential for adverse effects on skin, GIT, haematopoietic system, bones, phosphate homeostasis, ovaries, and liver at clinically relevant exposures.
- There was no evidence that trametinib has genotoxic potential. Carcinogenicity was not examined, consistent with ICH guidelines.
- The reproductive toxicity studies on trametinib indicate a potential for foetal and developmental toxicity. Pregnancy Category D is recommended.

Dabrafenib/Trametinib combination therapy

The primary pharmacology data confirm the efficacy of dabrafenib/ trametinib combination treatment in vitro and in vivo at clinically relevant dose levels.

The toxicity study with combination dabrafenib/trametinib treatment in dogs produced adverse effects consistent with treatment with either drug alone at the same dose levels.

Recommendation

- Based on the nonclinical data evaluated in this report, registration of trametinib is supported, provided clinical efficacy and safety can be demonstrated.
- Based on the nonclinical data evaluated in this report, registration of dabrafenib/trametinib combination is supported.
- The draft PI should be amended as indicated in this report.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Clinical rationale

Therapeutic options for unresectable and metastatic melanoma are limited. Chemotherapy including agents such as imidazole carboxamide and carboplatin have limited efficacy with only 10 to 15% of patients achieving any degree of tumour regression. More recently vemurafenib a selective BRAF inhibitor has demonstrated a worthwhile clinical benefit and another agent ipilimumab a mono-clonal antibody that blocks the cytotoxic T-lymphocyte antigen CTLA-4 has demonstrated significant improvement in OS of patients with metastatic melanoma. Nevertheless the need for further agents of worthwhile activity is clear and recognising that 60% of cutaneous melanomas have specific mutations of the BRAF oncogene which activates MEK in a downstream MAP kinase signalling cascade, by interfering with this pathway at the level of the MEK kinases represents an alternative and potentially clinically active treatment option for unresectable for metastatic BRAF mutant melanoma with a different safety profile.

Contents of the clinical dossier

Scope of the clinical dossier

The dossier contains four study reports with appropriate tabular summaries for the clinical pharmacology studies MEK111054 an open label multi-dose escalation study to investigate the safety, PK and pharmacodynamics (PD) of the MEK inhibitor trametinib in solid tumours or lymphoma; study MEK113709 an open label 2 period randomised cross over study to evaluate the effect of food on the single dose PK of the MEK inhibitor Trametinib in subjects with solid tumours; MEK113708 an open label mass balance study to investigate the ADME of a single oral dose of MEK inhibitor 14C Trametinib in male subjects with solid tumours; study MEK115064 to determine the absolute bioavailability of Trametinib following a single oral dose co-administered with an intravenous regular labelled micro-dose of Trametinib in subjects with solid tumours: study MEK113583 an open label multi-centre Phase II study to investigate the objective response rate, safety and PK of Trametinib in BRAF mutation-positive melanoma subjects previously treated either with or without a BRAF inhibitor: the Phase III pivotal study MEK114267 which is a randomised open label study comparing trametinib to chemotherapy in subjects with advanced metastatic BRAF V600 E-K mutation-positive melanoma: study BRF113220 an open label dose escalation Phase I/II study to investigate the safety, PK, PD and clinical activity of the BRAF inhibitor dabrafenib in combination with trametinib in subjects with BRAF mutant metastatic melanoma. Another PK study not relevant to this submission is MEK112111 a phase IB combination study of BRAF inhibitor trametinib with gemcitabine in subjects with solid tumours.

Full study reports together with relevant summaries for the three efficacy/safety studies MEK114267 the pivotal trial together with the two supportive studies MEK113583 a Phase II trial and MEK111054 a Phase I dose escalation study.

The relevant study evaluating the combination of trametinib and dabrafenib is Study BRF113220 a randomised Phase I/II open label study containing four parts including a full report regarding efficacy and safety.

Table 5: Studies relevant to this application

Study ID	Phase	Study drug/s	Population	Endpoints / comments
MEK111054	1	trametinib	Solid tumours, lymphomas	FTIH; dose escalation; anti-tumour activity.
MEK113709	1	trametinib	Solid tumours	Food effect
MEK113708	1	trametinib	Solid tumours	Mass balance
MEK115064	1	trametinib	Solid tumours	Absolute bioavailability
MEK113583	2	trametinib	BRAF mutant melanoma, 2nd line	PK, efficacy, safety.
MEK114267 "METRIC"	**3**	**trametinib versus chemotherapy**	BRAF V600E/K mutant advanced melanoma	PK, efficacy, safety. **Pivotal for monotherapy.**
BRF113220 Part A	1-2	trametinib, dabrafenib[A]	BRAF mutant melanoma	PK/interaction study
BRF113220 Part B	1-2	trametinib, dabrafenib[A]	BRAF mutant melanoma or colorectal cancer	PK, dose escalation
BRF113220 Part C	**2**	**dabrafenib[A] + trametinib versus dabrafenib[A]**	BRAF V600E/K mutant advanced melanoma	**Pivotal for combination therapy.**
BRF113220 Part D	1-2	dabrafenib[B]; dabrafenib[B] + trametinib	BRAF mutant melanoma	PK

[A] gelatin capsule; [B]HPMC capsule (commercial dabrafenib uses the HPMC capsule)
Some aspects of BRF113220, unrelated to combination therapy, were evaluated in the CER for dabrafenib (PM-2012-02231-3-4).

Paediatric data

This submission does not include paediatric data.

Good clinical practice

All aspects of good clinical practice have been observed in the study submitted.

For the remainder of this submission the evaluation will be presented in two parts. Both parts will relate to efficacy, safety and benefit/risk assessments; however, they are separated into evaluation of:

1. Trametinib monotherapy; and
2. Dabrafenib/trametinib combination therapy.

Trametinib monotherapy

Pharmacokinetics/Pharmacodynamics

Studies providing pharmacokinetic/pharmacodynamics data

A total of six PK/PD studies in relation to trametinib monotherapy have been provided in this submission and include Study MEK111054, Study MEK113709, Study MEK113708, Study MEK115064, Study MEK113583 and Study MEK114267 the pivotal Phase III study. These are indicated in Table 1 of Attachment 2. A comparison of results across the studies allows for further definition of the various PK parameters.

Dosage selection for the pivotal studies

Dose selection for the Phase II and III monotherapy studies was based on the results from Study MEK111054 in which the daily dose of trametinib ranging from 0.125 to 4 mg were administered to subjects with solid tumours. As discussed earlier a dose of 2 mg administered once daily was selected based on tolerability, exposure-response relationship with PD markers in tumour biopsies and clinical activity.

It is also noteworthy that MAP kinase pathway inhibition appeared to be dose dependent as demonstrated by modulation and tumour PD markers. The greatest inhibition was observed at 2 mg once daily the highest dose level tested. The mean trametinib concentrate observed following repeat dose administration of 2 mg once daily exceeds the pre-clinical target concentration of 10.4 ng/mL over the 24 hour dosing interval thereby providing sustained inhibition of the MEK pathway.

It is also worth noting that although not specifically significant 2.5 mg trametinib was not clearly more efficacious than 2 mg. In terms of clinical activity among BRAF V600 mutation-positive melanoma subjects, administration of trametinib doses of 2.5 mg or higher was not more efficacious than 2 mg with a complete and partial response rate (RR) of 36% (five of 14) of patients at 2.5 mg once daily compared to 44% (seven of 16) of patients at 2 mg once daily.

Efficacy

Studies providing efficacy data

The principle evidence supporting efficacy data for trametinib in the treatment of advanced stage metastatic melanoma comes from the pivotal Phase III Trial MEK114267 with supportive data available from the Phase II Study MEK113583 and additional data also available from 30 patients in the Phase I Study MEK111054. These studies are summarised in Table 6.

Table 6: Overview of studies evaluating the efficacy of trametinib in metastatic melanoma

Study	MEK114267	MEK113583	MEK111054
Level of Evidence	Pivotal	Supportive	Supportive
Critical Design Features	Phase III Randomized (2:1)[a]; stratified for LDH (≤ULN and >ULN) and prior chemotherapy (yes vs. no) Open-label Two-arm; active control Multicenter	Phase II Open-label Single-arm (2 Cohorts) Multicenter	Phase I FTIH study (dose escalation, determination of RP2D) Open-label Multicenter
Study Population	Subjects with BRAF V600E or K mutation-positive, unresectable or metastatic melanoma; previously untreated, or treated with 1 prior chemotherapy regimen	Subjects with BRAF mutation-positive (i.e., V600E, K, or D) metastatic melanoma previously treated with BRAF inhibitor (**Cohort A**) or not previously treated with BRAF inhibitor (**Cohort B**)	Subjects with solid tumors (e.g., melanoma, pancreatic cancer, CRC, and NSCLC), not responsive to standard therapies or for whom there was no approved or curative therapy
Prior Anti-Cancer Therapy	No prior BRAF or MEK inhibitor therapy A maximum of 1 prior chemotherapy regimen	No prior MEK inhibitor therapy No prior BRAF inhibitor therapy (Cohort B only) No inclusion criteria restrictions on number of prior chemotherapy regimens	No prior MEK inhibitor therapy; no restrictions on prior BRAF therapy No inclusion criteria restrictions on number of prior chemotherapy regimens
BRAF mutation testing[b]	Central	Local	Local
Number of subjects	322 subjects Trametinib arm: 214 subjects Chemotherapy arm: 108 subjects	97 Subjects Cohort A: 40 subjects Cohort B: 57 subjects	206 subjects (including 81 subjects with melanoma; 30 of the 81 subjects had BRAF mutation-positive melanoma not previously treated with BRAF inhibitors)
Location	North America, Europe, Australia New Zealand and South America	US and Australia	US
Efficacy endpoints			
Primary	PFS in subjects with BRAF V600E mutation, and no prior brain metastases (Primary Efficacy Population)	ORR	Efficacy was a secondary endpoint in this study (see below)
Secondary	PFS in ITT and subpopulations OS in Primary and ITT ORR in Primary and ITT Duration of response	PFS Duration of response OS	ORR PFS Duration of response

Study	MEK114267	MEK113583	MEK111054
Efficacy Assessment Schedule	At baseline, and at Weeks 6, 12, 21, and 30; and then, every 12 weeks till disease progression; and every 12 weeks following post disease progression	At baseline, and every 8 weeks thereafter until disease progression, start of new anti-cancer therapy, withdrawal of consent, or death	At baseline, and every 8 weeks thereafter until final study visit
Assessment Measure	RECIST v 1.1 of scans (CT/MRI) Investigator assessment for primary efficacy analysis	RECIST v 1.1 of scans (CT/MRI, chest X-rays) Investigator assessment for primary efficacy analysis	RECIST v 1.0 of scans (CT/MRI, bone scan, X-rays); investigator assessments
Module location	m5.3.5.1	m5.3.5.2	m5.3.5.2

Abbreviations: BRAF=proto-oncogene B-Raf; CRC=Colorectal cancer; CT=computed tomography; FTIH=First-time-in-human; ITT=intent-to-treat; LDH=lactate dehydrogenase; MR=magnetic resonance imaging; NSCLC=Non-small cell lung cancer; ORR=Overall response rate; OS=Overall survival; PFS=Progression free survival; RECIST=Response Evaluation Criteria In Solid Tumors; RP2D=Recommended Phase II dose; ULN=uppler limit of normal.

a. Subjects randomized 2:1 to receive trametinib vs. chemotherapy.

b. Subjects with histologically confirmed BRAFV600E/K mutation-positive metastatic melanoma (Stage IV) were enrolled into the studies MEK114267 and MEK113583; melanoma subjects in MEK111054 were not restricted by BRAF mutation status at enrolment. In Study MEK114267, tumor BRAF mutation status was determined using an allele-specific, investigational-use only polymerase chain reaction assay at Response Genetics Inc. (Los Angeles, CA, US). This assay specifically differentiates between the BRAF V600E and V600K mutant forms. Subsequently, a companion diagnostic assay has been developed and validated. Clinical validation to support licensure comes from the Phase III study MEK114267.

Evaluator's overall conclusions on efficacy of trametinib monotherapy

The data from the pivotal study and supportive studies certainly show evidence of a clinically significant benefit in relation to progression free survival (PFS) for patients with BRAF mutation-positive metastatic melanoma compared to patients who received chemotherapy. This was in evidence across all sub-groups though it is noted that the level of benefit for patients with BRAF V600K mutation-positive melanoma was not as great as that observed for the BRAF V600E mutation-positive patients and although the PFS favoured the patients receiving trametinib it did not reach clinical significance. Secondary efficacy end points including OS and overall response rate (ORR) also favoured the trametinib treated patients and were statistically significant for the ITT population and for the BRAF V600E mutation-positive melanoma patients, but it is again noted that the ORR for patients with BRAF V600K mutation positive melanoma had an inferior ORR compared to the chemotherapy arm.

The supportive studies supported the degree of response observed in the pivotal trial for the ITT population. As the pivotal study was quite a large well conducted trial there is definite evidence of benefit for trametinib in patients with BRAF mutation-positive melanoma but some further assessments are required in relation to the BRAF V600K mutation-positive patients to be confident that the benefits for these patients are comparable to those with BRAF V600E mutation-positive disease.

Safety of trametinib monotherapy

Studies providing safety data

The safety data provided in this evaluation is derived from three studies, namely the pivotal Study MEK114267 together with supportive data from Studies MEK113583 and MEK111054 with the safety population totalling 329 patients from these three studies all of whom received at least one dose of trametinib and in the instance of Study MEK111054 had a starting dose of 2 mg trametinib per day.

Adverse events (AEs) for the three studies were described according to standard criteria and graded according to WHO toxicity criteria.

Summary of patient/drug exposure

Three patients randomised to trametinib in the pivotal study were excluded from the integrated safety population because they did not receive at least one dose of study medication. Nine patients randomised to chemotherapy were also excluded for the same reason. Summary of the duration of exposure to trametinib and chemotherapy for the patient populations is indicated in Table 7.

Table 7: Summary of duration of exposure to trametinib or chemotherapy (safety population)

	MEK114267		Integrated Safety Population
	Chemotherapy (N=99)	Trametinib (N=211)	Trametinib (N=329)
Time on study treatment (months)[a]			
Mean	3.56	5.63	5.34
SD	3.244	3.923	4.339
Median	2.07	4.83	3.84
Min.	0.1	0.3	0.0[b]
Max.	14.0	16.3	24.5
Number of Subjects (%)			
≤2 months	46 (46)	39 (18)	84 (26)
>2 to ≤4 months	22 (22)	51 (24)	84 (26)
>4 to ≤6 months	12 (12)	43 (20)	54 (16)
>6 months	19 (19)	78 (37)	107 (33)

Data Source: 120-final Table 8.1, and MEK114267 120-final Table 8.714
Abbreviations: SD=Standard deviation
a. Time on study treatment is the time from the first dose date to last dose date including interruptions.
b. 1 subject received treatment for 1 day = 0.03 month.

In the pivotal study the median duration of trametinib treatment exposure was more than twice as long compared with the median duration of chemotherapy exposure at 4.8 months versus 2 months respectively. The mean daily dose of trametinib received in the pivotal study was 1.81 mg/m^2 as indicated in Table 8.

Table 8: Summary of exposure to trametinib or chemotherapy (safety population)

	MEK114267			Integrated Safety Population
	Dacarbazine (N=62)	Paclitaxel (N=37)	Trametinib (N=211)	Trametinib (N=329)
Trametinib daily dose (mg)[a] or Chemotherapy dose intensity (mg/m²/cycle)				
Mean	974.72	173.19	1.81	1.85
SD	75.419	6.564	0.295	0.264
Median	1000.00	175.00	2.00	2.00
Min.	562.5	147.0	0.8	0.8
Max.	1000.0	175.0	2.0	2.1
Number of Cycles, n (%)				
Min.	1	1	NA	NA
1st quartile	2	2	NA	NA
Median	3.0	2.0	NA	NA
3rd quartile	8	5	NA	NA
Max.	20	14	NA	NA
Number of Subjects (%)				
1-2 cycles	27 (44)	19 (51)	NA	NA
3-4 cycles	11 (18)	7 (19)	NA	NA
5-6 cycles	7 (11)	2 (5)	NA	NA
> 6 cycles	17 (27)	9 (24)	NA	NA

Data Source: 120-final Table 8.1, MEK114267 120-final Table 8.2
Abbreviations: NA=Not applicable, SD=Standard deviation
a. Daily dose is the cumulative dose divided by the duration of exposure.

Deaths

As indicated in Table 9, 157 patients or 48% treated with trametinib died with the most common reason being progressive disease. Only one patient had a death considered potentially related to trametinib therapy with the death being renal failure.

Table 9: Summary of deaths for MEK114267 and the integrated trametinib safety population

	MEK114267

Serious adverse events

As indicated in Table 10, serious AEs (SAEs) occurred in 22% of patients in the integrated drug trametinib safety population with cellulitis being the most common AE followed by pulmonary embolism, anaemia, dyspnoea, pneumonitis, vomiting, dehydration and erysipelas.

Table 10: Summary of serious adverse events reported by ≥ 2 subjects in either treatment arm of MEK114267 or in the integrated trametinib safety population

Preferred term	MEK114267		Integrated Safety Population
	Chemotherapy (N=99) n (%)	Trametinib (N=211) n (%)	Trametinib (N=329) n (%)
Any event	20 (20)	50 (24)	74 (22)
Cellulitis	0	4 (2)	9 (3)
Pulmonary embolism	0	3 (1)	7 (2)
Anaemia	2 (2)	3 (1)	4 (1)
Dyspnoea	0	3 (1)	4 (1)
Pneumonitis	0	4 (2)	4 (1)
Vomiting	1 (1)	3 (1)	4 (1)
Dehydration	1 (1)	1 (<1)	3 (<1)
Erysipelas	0	3 (1)	3 (<1)
Alanine aminotransferase increased	0	2 (<1)	2 (<1)
Back pain	0	1 (<1)	2 (<1)
Decreased appetite	0	1 (<1)	2 (<1)
Diarrhoea	1 (1)	1 (<1)	2 (<1)
Ejection fraction decreased	0	2 (<1)	2 (<1)
Endocarditis	0	1 (<1)	2 (<1)
Infection	0	2 (<1)	2 (<1)
Interstitial lung disease	0	2 (<1)	2 (<1)
Nausea	1 (1)	1 (<1)	2 (<1)
Pleural effusion	0	2 (<1)	2 (<1)
Pneumonia	1 (1)	0	2 (<1)
Pyrexia	4 (4)	1 (<1)	2 (<1)
Rash	0	2 (<1)	2 (<1)
Renal failure	0	2 (<1)	2 (<1)
Retinal vein occlusion	0	2 (<1)	2 (<1)
Cholecystitis	2 (2)	0	0

Data Source: 120-final Table 8.25

Those SAEs considered by the investigator to be related to the investigational drug occurred in 33 patients in the integrated treatment safety population and 26 in the pivotal study with the relevant causes indicated in Table 11.

Table 11: Summary of drug-related serious adverse events by > 1 subject in either treatment arm of MEK114267 or in 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 SAE	11 (11)	26 (12)	33 (10)
Pneumonitis	0	4 (2)	4 (1)
Cellulitis	0	0	2 (<1)
Dehydration	1 (1)	1 (<1)	2 (<1)
Ejection fraction decreased	0	2 (<1)	2 (<1)
Interstitial lung disease	0	2 (<1)	2 (<1)
Rash	0	2 (<1)	2 (<1)
Retinal vein occlusion	0	2 (<1)	2 (<1)
Pyrexia	3 (3)	1 (<1)	1 (<1)

Data Source: 120-final Table 8.24

Evaluator's overall conclusions on safety of the trametinib monotherapy

A sizeable spectrum of AEs has been reported from these studies for trametinib with the most common being skin rash, diarrhoea, fatigue, peripheral oedema, nausea and

vomiting. Nevertheless while more than 40% of these AEs were at least of Grade III[19] severity, few patients required drug withdrawal and were managed with appropriate dose interruption or dose reduction. It is noted that 92% of patients were able to continue trametinib until disease progression. Certain AEs require careful monitoring particularly potential for LVEF reduction and left ventricular dysfunction, visual impairment and rash. Less common, but also important potential AEs requiring appropriate monitoring included pneumonitis, hepatic events and hypertension. In general terms despite this incidence of AEs, some 92% of patients were able to complete their trametinib therapy.

First round benefit/risk assessment of trametinib monotherapy

First round assessment of benefits

The data from the three relevant clinical trials provided in the submission in relation to efficacy namely, the pivotal Study MEK114267, the Phase II Study MEK113583 and the Phase I/II Study MEK111054 have demonstrated a definite degree of efficacy for trametinib in patients with advanced/metastatic BRAF V600 mutation-positive melanoma. In the pivotal study the PFS benefit is highly significant with a median PFS for trametinib patients of 4.8 months compared to the chemotherapy arm of 1.4 months, representing a 55% improvement. This data was confirmed by both investigator assessments and independent review. Various sub-group analyses confirmed this benefit. Similarly, secondary efficacy parameters including OS, ORR and duration of benefit are all statistically significant in favour of trametinib. The supportive studies demonstrated RRs comparable to the pivotal study and again supportive of benefit for trametinib.

It is of particular note however that the patients with the V600K mutation-positive melanoma of which 54 patients were enrolled over the three studies, and 40 in the pivotal study of whom 37 patients received trametinib that the ORR for these patients receiving trametinib was lower at 10% compared to chemotherapy at 24%. Further although the median PFS for patients with V600K mutation-positive melanoma was in the order of 4.8 months compared to 1.5 months for those receiving chemotherapy, this did not reach statistical significance (p=0.0788). It is also noted that in the supportive Study MEK113583 that there were no objective responses among the eight patients with BRAF V600K mutation-positive melanoma who received trametinib. While it is recognised that there are relatively small numbers of patients involved in this sub-population it remains uncertain that the level of efficacy for trametinib in patients with V600K mutation-positive melanoma is comparable to that for patients with V600E mutation-positive melanoma.

Accordingly, it is appropriate to feel confident the benefits of trametinib are apparent for patients with V600E mutation-positive melanoma but remains less clear for those with V600K mutation-positive melanoma.

First round assessment of risks

The three studies provided in this submission for assessment of safety involving trametinib at a dose of 2 mg once daily demonstrated a definite spectrum of AEs with the most common being rash, diarrhoea, hypertension, peripheral oedema and fatigue. While these were often Grade I and II in severity nevertheless approximately 47% of patients did have Grade III toxicity, although there was a much lower proportion of Grade IV toxicities at 8% and only one death which was attributed to trametinib therapy, namely renal failure. There was however clear indication of other more serious AEs related to skin-

[19] Common Terminology Criteria for Adverse Events: Grade 1: Mild, asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; Grade 2: Moderate, minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living; Grade 3: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self- care activities of daily life; Grade 4: Life-threatening consequences; urgent intervention indicated; Grade 5: Death related to adverse event.

related toxicities, visual disorders, cardiac related events, hepatic events and pneumonitis all of which will require very careful monitoring.

Despite the spectrum of AEs, trametinib represents an agent with toxicities which are generally comparable to standard chemotherapy and BRAF inhibitors such as vemurafenib. These AEs have generally been adequately managed with appropriate monitoring, prophylaxis and early intervention.

Overall it is considered that the benefit-risk balance for trametinib in the treatment of V600 mutation-positive advanced/metastatic melanoma favours benefit in terms of worthwhile clinical efficacy as determined by improvements in PFS, OS and ORR. This particularly applies to the V600E mutation-positive patient population but remains somewhat less certain with regard to the V600K mutation-positive melanoma population. Accordingly consideration may need to be given to the recommendation regarding authorisation which will be discussed further below.

Dabrafenib/trametinib combination therapy

Trametinib is an allosteric inhibitor of MEK in the MAP kinase pathway. Studies discussed above have demonstrated clinically significant activity for this agent in the treatment of advanced/metastatic V600 mutation-positive melanoma. Dabrafenib is a small molecule ATP competitive inhibitor of BRAF and studies have demonstrated clinical efficacy in the treatment of advanced/metastatic V600 mutation-positive melanoma. As these two agents have a different mechanism of action it is considered that the combination of the agents may well represent a further advancement in the treatment of this difficult malignancy. Accordingly the Phase I/II Study BRF113220 was undertaken to assess the potential efficacy and safety of this drug combination. The study was undertaken in four parts:

- Part A involved eight patients and evaluated PK.
- Part B involved 80 patients who enrolled in an escalating dose cohort of dabrafenib and trametinib in a 3 plus 3 design.
- Part C which involved 162 patients was a randomised open label 3 arm study of dabrafenib/trametinib combination therapy with comparison to dabrafenib monotherapy in patients with metastatic BRAFV600 mutation-positive melanoma who were BRAF inhibitor naive.
- Part D involved assessment of a newer form of dabrafenib capsule (HPMC capsules) compared to the initial gelatine capsules which were used in the first three parts of the study.

Pharmacokinetics of dabrafenib/trametinib combination therapy

Part A of the study was designed as an open label study evaluating the effect of repeat dose of trametinib on the PK single dose dabrafenib. It is noted that trametinib has shown the highest inhibitory potential against CYP2C8 in vitro with the concentration resulting in 50% of maximum inhibition of 0.34 μmols but the risk of drug to drug interaction was considered low in vitro studies have demonstrated that the oxidative metabolism of dabrafenib was mediated by CYP2C8 and could potentially be affected by CYP2C8 inhibitors. Accordingly, subjects received a single 75 mg dose of dabrafenib as gelatine capsules on Day 1 with trametinib 2 mg once daily being administered from Day 2 through to Day 15. PK samples for determination of plasma dabrafenib were taken for up to 24 hours after the dabrafenib single dose on Days 1 and 15.

Part B was designed as an open label dose escalation repeat dose study to identify the range of tolerated dose of the dabrafenib/trametinib combination in patients with BRAF mutation-positive melanoma. The initial dose of the combination was half the

recommended dose of each agent. Doses of trametinib at 1, 1.5 and 2 mg once daily were administered in combination with dabrafenib at 75 or 150 mg twice daily as gelatine capsules using a dose escalation procedure. PK samples for determination of plasma concentration of trametinib, dabrafenib and dabrafenib metabolites were obtained for up to eight hours on Day 15 and Day 21. A dose proportionality of trametinib was evaluated using a power model.

Part D of the study involved evaluation of the PK of dabrafenib administered as HPMC capsules as monotherapy and combination after single and repeat doses. Patients were randomised to one of four treatment groups, that is, dabrafenib 75 or 150 mg twice daily monotherapy or in combination with trametinib 2 mg once daily. Serial PK blood samples were drawn after the first dose on Day 1 and after repeat dose on Day 21.

When administered in combination with trametinib, dabrafenib PK characteristics are similar to that when administered alone with a median T_{max} of 1.5 to 2 hours; T½ of 3.6 hours. Consistent with monotherapy, data exposure decreases to repeat twice daily dosing.

When administered in combination with dabrafenib, trametinib PK characteristics are similar to that when administered alone with a median T_{max} of 1.5 to 2 hours and it accumulates with repeat daily dosing.

Dose selection for the pivotal studies

Dabrafenib 150 mg twice daily and trametinib 2 mg once daily are recommended monotherapy dosing regimens for the treatment of patients with unresectable metastatic melanoma with BRAFV600 mutation. The relationship between exposure and response has been evaluated as indicated above. Dabrafenib and trametinib administered as full monotherapy doses in Part B of the study were well tolerated as will be discussed below and have been subsequently used in Part C of the study.

Efficacy of dabrafenib/trametinib combination therapy

The Phase I/II Study BRF113220 represents the evidence submitted for consideration of efficacy in relation to the dabrafenib/trametinib combination. Part C represents the pivotal component in which data from a randomised Phase II three arm open label study evaluated the safety and efficacy of a dabrafenib/trametinib combination therapy with comparison to dabrafenib monotherapy. This phase of the study enrolled 162 BRAF inhibitor naïve patients who were randomised according to 54 patients of dabrafenib 150 mg twice daily plus trametinib 2 mg, 54 patients to dabrafenib 150 mg twice daily plus trametinib 1 mg and 54 patients to dabrafenib monotherapy at 150 mg twice daily alone.

Supportive data also came from Part B of the study which is a dose escalation and safety/efficacy expansion phase and Part D in which the HPMC capsules were evaluated and this is outlined in Table 12.

Table 12: Overview of studies evaluating the efficacy of combination dabrafenib/trametinib in unresectable and/or metastatic BRAF V600 mutation-positive melanoma

Study	BRF113220 Part C	BRF113220 Part B	BRF113220 Part D
Critical Design Features	Randomized, open-label	Dose-escalation and safety/efficacy expansion	Randomized, open-label
Prior Anti-Cancer Therapy	No prior BRAF or MEK inhibitor therapy Up to one regimen of chemotherapy and/or IL-2 in the metastatic setting	No prior BRAF or MEK inhibitor therapy Previous BRAF inhibitor therapy (expansion cohort)	No prior BRAF inhibitor therapy
BRAF mutation	BRAF V600-positive (V600E, V600K or V600D)	BRAF V600-positive (V600E, V600K or V600D)	BRAF V600-positive (V600E or V600K)
Dabrafenib Capsule Type	Gelatin[a]	Gelatin[a]	HPMC
Disease Assessment Schedule	Every 8 weeks	Every 8 weeks	Every 8 weeks
Number of subjects Study treatment	162 dabrafenib monotherapy: 54 Crossover to 150/2: 43 150/1 combination: 54 150/2 combination: 54	135[b] 150/2 combination: BRAFi-naive: 24 BRAFi-treated: 26	110[c] 150/2 combination: 39
Efficacy Endpoints			
Primary	PFS, ORR (CR + PR), Duration of Response	N/A	N/A
Secondary	OS	ORR (CR + PR)	ORR (CR + PR)

Abbreviations: BRAF=; BRAFi=BRAF inhibitor; CR=complete response; CPSR=clinical pharmacology study report; DTIC=dacarbazine; HPMC=hydoxypropyl-methylcellulose; IL-2=interleukin 2; ITT=intent to treat population; NA= not applicable; ORR=overall response rate; PFS=progression free survival; PR=partial response; subpops=subpopulations

a. Some subjects in Parts B and C received HPMC capsules for approximately 2 months, on average.
b. Additional dose groups include: 75/1 combination (n=6); 150/1 combination (n=22); and 150/1.5 combination (n=25). These results are reported in the BRF113220 CPSR.
c. Additional dose groups include: dabrafenib 75→75/2 (n=12); dabrafenib 150→150/2 (n=16); 75/2 combination (n=43). These results are reported in the BRF113220 CPSR.

Additional data was also provided from the Part C patients who crossed over from dabrafenib monotherapy to combination therapy.

Part B of the study enrolled patients in escalating dose cohorts of dabrafenib and trametinib in a 3 plus 3 design. The highest three cohorts, which are 150-1, 150-1.5 and 150-2 were expanded to a maximum of 25 subjects. Upon completion of dose escalation two additional efficacy expansion cohorts were opened with the relevant one being patients with BRAFV600 mutation-positive melanoma who had experienced disease progression following prior treatment with a small molecule BRAF inhibitor.

Part C was a Phase II randomised three arm open label evaluation of safety and efficacy of combination therapy with dabrafenib 150 mg twice daily and two different doses of trametinib 1 mg once daily and 2 mg once daily compared with dabrafenib monotherapy in patients with advanced BRAFV600 mutation-positive melanoma who are BRAF V600 naïve. Randomisation was to three arms according to that described above. Patients who had documented disease progression according to Response Evaluation Criteria in Solid Tumours (RECIST)[20] criteria on the dabrafenib monotherapy arm had the opportunity to cross over to the dabrafenib 150-2 combination therapy.

Three primary efficacy end points were specified, namely, PFS, ORR and duration of response with OS identified as a secondary end point. Disease assessments were conducted every eight weeks. Patients who continued were followed till death.

[20] Response Evaluation Criteria In Solid Tumors (RECIST) is a set of published rules that define when tumours in cancer patients improve ("respond"), stay the same ("stabilise"), or worsen ("progress") during treatments.

It is to be noted that Part C was initially designed as a non-randomised expansion cohort based on dose identified in Part B with planned enrolment of approximately 20 patients per dose cohort. The protocol was amended prior to the initiation of Part C to a randomisation of dabrafenib monotherapy arm. An initial 20 patients per arm were planned but this was subsequently increased to 50 patients per arm. A blinded and independent review committee (BIRC) was also introduced. Several sensitivity analyses were also pre-specified.

It is to be noted that Part D of the study involving the HPMC capsule formulation was undertaken because of the prior use of gelatine capsules for Part B and Part C of the study as appropriate to evaluate the PK and safety profiles of the combination utilising the HPMC capsule. The PK data has already been presented above. The safety data will be presented subsequently.

Evaluator's overall conclusions on efficacy of dabrafenib/trametinib combination therapy

The data from Part C of the study shows statistically significant improvement in PFS for the 150/2 combination compared to the dabrafenib monotherapy with a 61% reduction in risk of tumour progression or death and a median PFS of 9.4 months compared to 5.8 months for monotherapy. It is noted the BIRC also demonstrated similar degrees of significant benefit. However the investigator evaluation suggested a statistically significant benefit also for the 150/1 combination that was not confirmed by the BIRC. There was also a statistically significant improvement in ORR in Part C patients with the 150/2 combination with an ORR of 76% compared to 54% for the dabrafenib monotherapy group. Again no such benefit was seen for the 150/1 combination. Data for duration of response also confirmed this benefit. Nevertheless the OS data remains immature.

While this data shows promise in that the median PFS for the combination represents an advance on that seen for dabrafenib monotherapy in the randomised study as well as improvement compared to the trametinib monotherapy from the studies discussed above there remain a number of concerns regarding the studies.

The number of patients involved in the trials still remains relatively small with only 54 patients receiving the combination and a similar number in the monotherapy group. Further the design of the study involved a number of amendments to ultimately provide a randomised evaluation. Appropriately the study is classified as a Phase II trial and in this instance the comparative data between the combination and monotherapy remains inconclusive. The follow up durations for the study are also relatively short and nearly 50% of patients still remain on treatment and more than 50% in follow up. Accordingly the level of benefit for the combination remains uncertain.

Safety of the dabrafenib/trametinib combination therapy

Studies providing safety data

Safety evaluation for this submission comes from the Study BRF113220 which involved those patients receiving treatment with the combination of dabrafenib 150 mg and trametinib 2 mg and involved 202 patients with BRAF mutation-positive melanoma from Part B, C and D of Study BRF113220. These data were compared with the trametinib monotherapy material described in the earlier part of this evaluation involving the three studies MEK114267, MEK113583 and MEK111054, and 329 patients. Comparison was also made with the dabrafenib monotherapy safety update population involving 586 patients with melanoma treated with 150 mg twice daily of dabrafenib across five studies. Accordingly the various safety populations involved in the evaluation are indicated in Table 13.

Table 13: Integrated Summary of Safety (ISS) safety populations and designations

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

The median time on study treatment with dabrafenib was longer for the Part C 150/2 group compared with the Part C dabrafenib monotherapy group.

The median times on study treatment for the trametinib population and the dabrafenib population were about one half that for the Part C combined group but similar to the Part C dabrafenib monotherapy group. Accordingly the duration of exposure to both trametinib and dabrafenib in the combination is longer than for the single agents and indicates that the Part C 150/2 group represents the most appropriate group to assess the safety of the combination treatment. In the Part C 150/2 group the median daily dose of dabrafenib was 281.75 mg similar to the Part C dabrafenib monotherapy group at 295.91 mg and close to the targeted daily dose of 300 mg for both treatment groups. The median daily dose of trametinib 1.92 mg in the Part C 150/2 group is also close to the targeted daily doses of 2 mg.

All patients in the Part C 150/2 group had at least one AE and at least one drug-related AE. Most of these led to dose interruption and one half had AEs resulting in dose reduction. These data were greater than for the monotherapy treatment. The higher frequency of dose reductions and interruptions in the combination therapy group suggests a lower tolerability for combination therapy compared with each individual monotherapy.

Deaths and serious adverse events

For the combination group disease progression was the cause of death in 11 of 14 patients or 80% who died. Three patients or 5% in the Part C 150/2 population and seven patients or 3% in the pooled 150/2 population died due to fatal AEs. Five patients or 2% in the trametinib population and eight patients in the dabrafenib safety population died due to fatal SAEs. All of these were not considered related to study drug with the exception of one event of ventricular arrhythmia which is considered related to both study drugs in a patient with a history of hypertension.

In the Part C 150/2 treatment group SAEs were reported by 62% of patients, with pyrexia and chills being the most common. Approximately 11% of these patients required hospitalisation for SAEs of pyrexia which compared with only one patient in the dabrafenib monotherapy group who required hospitalisation for pyrexia.

Evaluator's overall conclusions on safety of dabrafenib/trametinib combination therapy

These combination data reflect essentially a similar safety profile to the monotherapies making up the combination, namely dabrafenib/trametinib. Nevertheless certain toxicities

occurred with a higher frequency most particularly pyrexia and to a lesser extent fatigue and nausea occurred at a higher frequency relative to dabrafenib and there was a higher incidence of fatigue, nausea and vomiting relative to trametinib monotherapy. There was however an apparent lower incidence of certain skin-related toxicities particularly keratoacanthomas (KA) and squamous cell carcinomas (SCC).

The most severe toxicity encountered was pyrexia requiring intensive intervention, both dose interruption and dose reduction were required in approximately 50% of patients and 5% of patients had to permanently discontinue therapy.

Accordingly although it is reasonable to indicate that in general terms monitoring, prophylaxis and early management of this AE profile for the combination would allow for its routine clinical use there needs to be an understanding that the toxicity profile for this combination is not insignificant.

With regards to the two capsule formulations for dabrafenib the available safety data indicated the increased exposure observed with the HPMC capsule shell has no significant impact on the combination safety profile compared to the gelatine capsules. Nevertheless it should be noted that this safety data were generated in three small treatment groups and were indirectly compared with differences in length of drug exposure.

First round benefit/risk-assessment of dabrafenib/trametinib combination therapy

First round assessment of benefit

Rationale for the development of the combination therapy and Study BRF113220 came from the fact that there was evidence that the active agents BRAF inhibitors particularly vemurafenib and dabrafenib and the MEK inhibitor trametinib while demonstrating worthwhile RRs and improvements in PFS were limited by the ultimate development of drug resistance and progression of disease generally within five to seven months of starting treatment. It is considered the combination of the two drugs with different mechanisms of action may result in improvement in outcomes.

Accordingly Study BRF113220 was designed involving four parts with Part A being essentially a PK evaluation in eight patients, Part B a dose escalation phase involving a total of 80 patients including 39 treated at the maximum tolerated dose (MTD) 150 mg dabrafenib twice daily and 2 mg trametinib daily. Part C was the randomised open label three arm study of the combination in 162 patients in which 54 patients were randomised to each of three arms including the combination 150/2 and the combination 150/1 and dabrafenib monotherapy at 150 mg twice daily. Part D involved evaluation of the HPMC capsule in a comparison of PK and safety to the older gelatine capsules. The principal area for determination of efficacy relates to Part C in which there is a significant improvement in PFS for the combination versus dabrafenib with an HR of 0.39 ($p<0.0001$) with an estimated median PFS for the combination 150/2 at 9.4 months compared to 5.8 months for the monotherapy and estimated PFS at 12 months of 41% for the 150/2 combination compared to 9% for the monotherapy. Independent review of these data confirmed the improvement and PFS. It is noted however that while the investigator assessment suggested significant improvement for the 150/1 combination with a significant advantage for PFS over monotherapy this was not determined by the independent review analysis. Overall, RRs also showed a significant improvement for the 150/2 combination at 76% including a 9% complete remission rate compared to a 54% ORR for the monotherapy with a 4% complete RR ($P=0.0264$). A significant benefit in ORR was not observed for the 150/1 combination.

It is worth noting that these impressive results particularly relate to the V600E mutation-positive population as although there were also advantages for the V600K mutation-positive population the numbers involved were small involving only seven patients.

These data therefore have certainly suggested a further benefit for the dabrafenib/trametinib combination over either monotherapy alone or other BRAF inhibitors and the antibody iplumibab. There are however several concerns with regards to this study namely the overall small number of patients in each arm of the study; the fact that the study was Phase II in type rather than Phase III and that much of the study design involved various adjustments prior to initiation of the study. There remained a significant proportion of patients still on treatment; 47% and 50% of the patients remain on study. The duration of follow up remains relatively short preventing any assessment at this time of OS.

First round assessment of risks

The safety profile provided in this evaluation essentially comes from that associated with Part C of Study BRF113220. The safety profile appears to be generally consistent with that to be expected in relation to the individual drugs involved in the combination although several of these toxicities were of a somewhat greater incidence than the monotherapy. This resulted in a higher incidence of dose reduction and dose interruption compared to monotherapy. Pyrexia related events were the largest contributor to this with 76% of patients experiencing pyrexia related events and 33% Grade III in severity. This resulted in an increased incidence of SAEs, hospitalisations, dose interruptions and 5% of patients requiring permanent discontinuation of study medication.

Despite this somewhat greater incidence of AEs it is recognised with appropriate monitoring, prophylaxis and early intervention this could generally be managed adequately.

It is noteworthy that the incidence and severity of other more significant AEs associated with the monotherapy including cardiac-related AEs, hypertension, hepatic disorders, diarrhoea and pneumonitis were not greater than for the individual drugs.

It is also noted that the safety data indicated the increased exposure observed with the dabrafenib HPMC capsule shell has no significant impact on the combination safety profile compared to the dabrafenib gelatine capsules so that doses utilised with the gelatine capsule can be reasonably transferred to HPMC dabrafenib capsule dosage.

First round assessment of benefit/risk balance

While the apparent benefits observed in the Study BRF113220 are impressive when compared with the monotherapy and suggest a further advance in therapies of potential value for advanced stage/metastatic KRAS mutation-positive melanoma there are sufficient deficiencies in the data as indicated above to maintain uncertainty as to this level of benefit.

It is noted that there are two major ongoing Phase III studies including Study MEK115306 which is a double blind randomised Phase III study comparing the dabrafenib/trametinib combination therapy at the 150 mg/2 mg dosage to dabrafenib administered with a trametinib placebo. Study MEK116513 is an open label randomised Phase III study comparing dabrafenib/trametinib combination therapy at the 150 mg/2 mg dosage with vemurafenib at 960 mg twice daily. These two studies should provide major supportive evidence in relation to the efficacy and safety of the combination. It is worth noting that the risk profile for the combination whilst somewhat greater than for the individual agents with appropriate monitoring, prophylaxis and early intervention should remain manageable providing the levels of efficacy presently indicated are confirmed.

First round recommendation regarding authorisation

The proposed indication in this submission is for marketing approval of Mekinist as a monotherapy and in combination with dabrafenib for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic Stage IV melanoma.

Mekinist as monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy.

This investigator maintains concerns with regard to the proposed indication in relation to monotherapy. While the data appears strong in relation to patients with BRAF V600E mutation-positive melanoma and therefore supportive of approval, the data in relation to BRAF V600K mutation-positive melanoma remains somewhat weak without evidence of response advantage or significant PFS advantage for the trametinib monotherapy when compared to chemotherapy.

In relation to the proposed combination as part of the indication as discussed above there are several areas of ongoing concern with regard to the submitted material and its adequacy to be confident of the apparent considerable improvement in further benefit for the dabrafenib/trametinib combination.

While this reviewer considers it very likely that these aspects will be resolved and remains supportive of trametinib for all patients with BRAF V600 mutation-positive unresectable metastatic melanoma and also the combination for the same proposed indication, it would seem prudent to await the results of the outstanding Phase III trials before authorisation.

List of questions

1. Further data is requested in regard to evidence of the level of benefit of trametinib in the treatment of patients with V600K mutation-positive advanced stage metastatic melanoma.
2. Further follow up for Study BRF113220 is requested.
3. Data from the outcomes of the two ongoing randomised studies, MEK115306 and MEK116513, are requested.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan identified as EU Risk Management Plan (EU-RMP) Version 0.0 (dated 31/01/2013, DLP 25/09/2012) with Australian Specific Annex (ASA) Version 1 (undated), which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the non-clinical aspects of the Safety Specification (SS) by the Toxicology area of the Office of Scientific Evaluation (OSE) and the clinical aspects of the SS by the Office of Medicines Authorisation (OMA), the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows (Table 14).

Table 14: Summary of Ongoing Safety Concerns

Summary of safety concerns	
Important identified risks related to trametinib monotherapy	Off-label use in patients with tumour progression during prior treatment with BRAF inhibitor therapy
Important identified risks related to trametinib monotherapy and dabrafenib/trametinib combination	Skin related toxicities (e.g., rash, PPES) Diarrhoea Cardiac-related events (e.g., LVEF decreased and left ventricular dysfunction) Ocular events (e.g., retinal vein occlusion, chorioretinopathy, and uveitis) Pneumonitis Hepatic events (AST, ALT, increased) Hypertension Oedema events (e.g., oedema peripheral) Hypersensitivity
Important identified risks related to trametinib when dabrafenib is added as combination therapy	Pyrexia Cutaneous SCC (cuSCC) Non-cutaneous secondary/recurrent malignancies New primary melanoma Renal Failure Pancreatitis Nausea and vomiting
Important potential risks related to trametinib monotherapy and dabrafenib/trametinib combination	Increased risk for dose adjustment and, when used in combination with dabrafenib, increased risk of serious adverse events in elderly population (≥65 years) Off-label use: in resectable/resected melanoma, in non-melanoma tumours harbouring a BRAF V600-mutation, use in combination with other anti-cancer agents, or when non-validated tests are used
Important potential risks related to dabrafenib/trametinib combination	Testicular toxicity
Important missing information related to trametinib and dabrafenib/trametinib combination	Use in patients with 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 Developmental toxicity and risks in lactation Use in patients with reduced cardiac function

Summary of safety concerns	
	Potential for QT prolongation Use in paediatric population (children less than 18 years) Risks in patients with ECOG 2-4 Ability to detect adverse reactions which are rare

Office of Product Review reviewer comment:

Notwithstanding the evaluation of the non-clinical and clinical aspects of the SS some additional ongoing safety concerns should be considered.

The sponsor should add the following as Ongoing Safety Concerns:

- Important Identified Risks: neutropaenia.

Pharmacovigilance plan

Proposed pharmacovigilance activities

The sponsor proposes routine pharmacovigilance activities for important identified and potential risks and missing information (as stated above). Furthermore, additional activities are planned for some of the risks. These activities are summarised in Table 15.

Table 15: Activities additional to routine planned by the sponsor regarding certain safety concerns

Additional activity	Assigned safety concern	Actions/outcome proposed	Planned submission of final data
Further investigation, Japanese subjects for first time in humans (MEK114784) (Phase I and Phase I/II, 1) Protocol available	Use in Non-White population	The aims of the study are to evaluate safety, tolerability, and PK of GSK1120212 single agent and to evaluate the safety, tolerability, PK, and efficacy of GSK1120212 dosed in combination with gemcitabine all in Japanese subjects with solid tumours	CSR expected 1st Q, 2014
Further investigation, QTc study (MEK114655) (Phase I,1) Protocol available	Potential for QT prolongation	To evaluate the effect of repeat oral dosing of trametinib on cardiac repolarization in subjects with solid tumours	Final CSR estimated April 2015
Exploratory research on MOA of pyrexia adverse event of special interest (pharmacogenetics study, 1) No protocol available	Pyrexia	To explore pharmacogenetic differences for subjects that experience pyrexia	Unknown (planned study only)
Trametinib PIP: EMEA-001177-PIP01-11 Dabrafenib PIP: EMEA-001147-PIP01-11	Use in paediatric population	To understand and collect additional information regarding use and safety in children.	

OPR reviewer's comments in regard to the pharmacovigilance plan and the appropriateness of milestones

The sponsor plans routine and additional pharmacovigilance activities. Only some safety concerns have been assigned an additional activity.

The available study protocols submitted are considered acceptable in regard to the assigned safety concern for RMP purposes.

The sponsor's proposed pharmacovigilance activities and milestones are considered acceptable, but not complete. Further recommendations are made below:

- **Unavailable study protocols:** There is neither a protocol, nor a protocol synopsis available for one planned study (Exploratory research on mechanism of action (MOA) of pyrexia adverse event of special interest). The sponsor should submit this as soon as it becomes available.
- **Suggested additional pharmacovigilance activities:** The sponsor should conduct studies or assign existing studies to the following Ongoing Safety Concerns:
  - Renal Failure;
  - Pancreatitis;
  - Neutropaenia;

- Use in patients with Class II, III, or IV heart failure;
- Safety in patients with severe renal impairment; and
- Safety in patients with moderate to severe hepatic impairment.

It is noted that the sponsor is conducting a study with regard to 'Safety in patients with moderate to severe hepatic impairment' in another jurisdiction.

Interactions and adverse event profile when co-administered with other agents:

Given the short term response rate of BRAF inhibitors, it has been suggested in the literature to combine BRAF inhibitors with agents with a long term response rate agent such as high-dose interleukin-2 (IL-2) or ipilimumab (Jang & Atkins, 2013[21]).

In section 'SVII.4 Identified and potential interactions', the sponsor makes no reference to data in regard to potential interactions of trametinib with other agents to treat melanoma (other than dabrafenib). Unless sufficient existing data is available, the sponsor should consider conducting a study (or assign this to an existing study) to investigate the safety profile of a combination of trametinib and other agents likely to be co-administered currently or in the future (such as IL-2 or ipilimumab).

Risk minimisation activities

The sponsor does not propose additional risk minimisation activities.

OPR reviewer comment: This is considered acceptable.

- **Potential for medication errors:** For the purposes of this RMP evaluation different types of medication errors, as suggested by Ferner & Aronson, 2006[22], have been considered.

  OPR reviewer comment: The sponsor's actions regarding name confusion, labelling and presentation are considered acceptable.

- **Potential for overdose:** The risk for overdose is low. In the proposed PI, overdosage and its management have been discussed to a satisfactory standard, with the exception of the clinical features that may observed in doses higher than recommended therapeutic doses (such as a description that retinal pigment epithelial detachment has occurred in patients on doses higher than currently recommended).
- **Potential for off-label use:** Trametinib could potentially be used to manage other conditions, including, but not limited to pancreatic cancer, Non-small-cell lung carcinoma (NSCLC), acute myeloid leukaemia, or chronic myelomonocytic leukaemia. The proposed indication is adequately described in the proposed PI, and this drug will be almost exclusively prescribed by oncology specialists, but there is a potential for off-label use.
- **Potential for paediatric off-label use:** The sponsor recognises that trametinib is only indicated for adults. This is reflected in the proposed PI. It is noted that the sponsor has a paediatric investigation plan in place for a possible future extension of indication to include a paediatric population.

21 Jang S, Atkins MB, 2013. Which drug, and when, for patients with BRAF-mutant melanoma? Lancet Oncol., 14:e60–69

22 Ferner RE, Aronson JK, 2006. Clarification of terminology in medication errors: definitions and classification. Drug Saf., 29:1011–1022.

Risk minimisation plan

The sponsor is planning routine risk minimisation activities. No additional risk minimisation activities are proposed for trametinib.

*OPR reviewer comment: T*rametinib as monotherapy or in combination with dabrafenib is associated with many AEs that require dose adjustment or drug cessation. As a result a baseline assessment and AE monitoring are essential and these need to be reflected in the proposed PI. Recommendations in regard to monitoring are already described in various parts of the proposed PI, but a separate table that outlines all the necessary monitoring actions should be added.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP (EU Risk Management Plan (EU-RMP) Version 0.0 (dated 31/01/2013, DLP 25/09/2012) with Australian Specific Annex (ASA) Version 1 (undated)) is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; the submitted EU-RMP is applicable without modification in Australia unless so qualified; and the draft PI and consumer medicine information (CMI) documents should NOT be revised until the Delegates Overview has been received:

- **Further safety considerations:** Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated request for further information and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

  Unless the sponsor can provide compelling justification against any of the following recommendations, the following should be considered:

- **Recommendations in regard to ongoing safety concerns:** The sponsor should add the following as Ongoing Safety Concerns
  - Important Identified Risks: Neutropaenia

- **Recommendations in regard to pharmacovigilance activities**: There is neither a protocol, nor a protocol synopsis available for one planned study (Exploratory research on MOA of pyrexia AE of special interest). The sponsor should submit this as soon as it becomes available.

  The sponsor should conduct studies or assign existing studies to the following Ongoing Safety Concerns:
  - Renal Failure;
  - Pancreatitis;
  - Neutropaenia;
  - Use in patients with Class II, III, or IV heart failure;
  - Safety in patients with severe renal impairment; and
  - Safety in patients with moderate to severe hepatic impairment.

Unless sufficient existing data is available, the sponsor should consider conducting a study (or assign this to an existing study) to investigate the safety profile of a combination of

trametinib and other agents likely to be co-administered currently or in the future (such as IL-2 or ipilimumab).

Recommendations in regard to monitoring are already described in various parts of the proposed PI, but a separate table that outlines all the necessary monitoring actions should be added.

Second round RMP advice

Comments on the safety specification of the RMP

Non-clinical evaluator's comments:

"The sponsor has provided the EU Risk Management Plan for trametinib together with an Australian Specific Annex. The results and conclusions drawn from the nonclinical program for trametinib detailed in the table on Key Safety Findings from Nonclinical Part of the Safety Specifications section of the Risk Management Plan (Section 1.13) are in general concordance with those of the nonclinical evaluator except that the following findings in the nonclinical program were not noted in the RMP:

- Soft tissue mineralisation and hypertrophy of epiphyseal growth plate in rats possibly secondary to perturbed phosphate and calcium homeostasis (elevated serum inorganic phosphorus)."

OPR reviewer comment: Given the target population of the drug, epiphyseal growth plate issues are unlikely to form an Ongoing Safety Concern at this stage. Soft tissue mineralisation due to elevated serum phosphorus levels associated with MEK inhibition may be of more concern. However, clinical studies did not report increased serum phosphorus levels. If elevated serum phosphorus levels appear as a signal, this may need to be investigated further.

Suggested wording for conditions of registration

Implement EU Risk Management Plan (EU-RMP) Version 0.0 (dated 31/01/2013, DLP 25/09/2012) with Australian Specific Annex (ASA) Version 1 (undated), and any future updates as a condition of registration.

Reconciliation of issues outlined in the RMP report

Table 16 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 16: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated TGA request for further information and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these include a consideration of the relevance for the Risk	'No safety considerations relevant to the RMP were raised by the non-clinical or clinical evaluators in the Section 31 reports. The company commits to addressing any safety considerations that might be raised during the procedure.'	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.		
The sponsor should add the following as Ongoing Safety Concerns: Important Identified Risks: • Neutropaenia	'Based on the adverse event data, neutropaenia is not a potential risk for trametinib monotherapy. For monotherapy, no cases of serious or Grade 3 or 4 neutropaenia events were reported. Neutropaenia of any grade was reported at a rate of less than 1%. Given the comorbidities of the enrolled subjects this rate is not unexpected. For combination therapy the company agrees, and therefore neutropaenia will be added to the RMP as an important identified risk (noting this aligns with the CHMP position). Suitable risk minimization measures and pharmacovigilance activities will be proposed. A draft of the updated EU-RMP will be available in mid-September (when the company responds to EU Day 120 questions), but will not be finalised until opinion is reached; which will be at the earliest in December 2013.'	This is considered acceptable.
There is neither a protocol, nor a protocol synopsis available for one planned study (Exploratory research on MOA of pyrexia AE of special interest). The sponsor should submit this as soon as it becomes available.	'The dabrafenib pharmacogenetics case control study BRF116604, Pharmacogenetic Evaluation of Pyrexia in Patients Receiving Dabrafenib (BRAF Inhibitor), is now complete and the study report synopsis is included below. The results from this study do not impact the current benefit/risk profile of dabrafenib/trametinib combination therapy, nor do they impact the risk management proposals for pyrexia. The results of this study are considered exploratory, requiring confirmation in future clinical trials and they are not actionable clinically.' The sponsor has provided a study report synopsis.	This is considered acceptable.
The sponsor should conduct studies or assign existing studies to the following Ongoing Safety Concerns: • Renal Failure; • Pancreatitis;	'In relation to the trametinib EU-RMP; Renal Failure and Pancreatitis are ongoing safety concerns only for the combination treatment. No specific studies are planned to address these safety issues in patients receiving combination therapy. **Trametinib:** Renal failure was identified in 6 (2%) subjects receiving described for these risks in the approved dabrafenib EU-RMP (also relevant to Australia), routine pharmacovigilance will be conducted along with targeted follow-up questionnaires (TFQ) for renal failure and	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
	increased lipase/pancreatitis, to collect structured data post-marketing to elucidate the frequency, severity and outcomes of these events. Risk minimization is based on communication through the product labelling and patient information leaflet. As renal failure and pancreatitis are AEss of special interest for all dabrafenib/trametinib combination studies, these events are followed and managed in real-time. GSK considers that the ongoing assessment of events of renal failure and pancreatitis in the clinical trials, along with the TFQs for post-marketing, will provide sufficient information to manage this safety concern. Therefore, no studies are planned to specifically address renal failure and pancreatitis in patients receiving combination therapy.' trametinib monotherapy, only 1 of which required dose interruption and none requiring dose reductions. Of the 3 events considered serious, all had clear confounding and other contributing factors for renal failure including dehydration, infection and extensive metastatic disease. Pancreatitis was identified in 1 (<1%) subject receiving trametinib monotherapy which required dose interruption but not dose reduction; this event was not an SAE. The totality of the data does not suggest a clear causal association between trametinib monotherapy and either renal failure or pancreatitis. **Dabrafenib/Trametinib combination:** In alignment with the pharmacovigilance measures.	
Neutropaenia;	'In relation to the trametinib EU-RMP and the response given to the TGA RMP question 2; Neutropaenia will be added as an identified risk for combination therapy but not for trametinib monotherapy. However, no studies are planned to specifically address neutropaenia in patients receiving combination therapy. Although there were 18 (9%) reports of neutropaenia, including 11 (5%) Grade 3/4 events in the pooled 150 mg twice daily dabrafenib/2 mg once daily trametinib population in the Integrated Summary of Safety (ISS), of these, only 2 events (<1%) were reported as SAEs. Events of neutropaenia infrequently resulted in dose interruption (3%) or dose reduction (<1%), and no subjects discontinued study drug due to neutropaenia. Thus, events of neutropaenia in this population are manageable with standard clinical practice. Neutropenia is evaluated in outputs from all clinical studies; in addition, SAEs from clinical studies are evaluated on an ongoing basis.'	This is considered acceptable.
Use in patients with Class II, III, or IV heart failure;	'GSK recognises the limitations in the current inclusion criteria with regards to cardiac risk factors, including Class II, III, or IV heart failure. The cardiac safety of trametinib monotherapy and combination treatments have not been characterised in patients with these conditions. Internal discussions to address these limitations are ongoing; if deemed necessary, GSK will conduct a study to evaluate and manage risk in these	It would not be unreasonable for the sponsor to include class II, III, or IV heart failure patients in an existing study. As a result the

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
	patients. It should be noted that the use of trametinib or the combination in patients with Class II, III or IV heart failure was raised by the EU regulators as part of the Day 120 questions. To address the EU RMP question, GSK is revising the Special Warnings and Precautions section of the proposed EU SmPC to make it clear that these patients were excluded from clinical trials and the safety of use in this population is therefore unknown. GSK can commit to adding similar language to the Australian PI.'	recommendation remains. The proposed PI change is supported by the RMP evaluator.
Safety in patients with severe renal impairment; and	'GSK does not propose to conduct a study for trametinib, however a study for dabrafenib is planned. **Trametinib:** There are no planned studies with trametinib in patients with severe renal impairment as renal excretion is not an important pathway of elimination for trametinib. Less than 19% of the excreted dose (or <10% of the radioactive dose) is 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. Results of the population PK analysis further support that renal impairment is unlikely to have a clinically relevant effect on trametinib PK. PK data from 223 (45.2%) and 35 (7.1%) subjects with mild (GFR 60 to <90 mL/min/1.73 m2) and moderate (GFR 30 to <60 mL/min/1.73 m2), respectively, were included in the population analysis. The GFR ranged from 41.5 to 226 mL/min/1.73 m2. The effect on trametinib CL/F and thus exposure was small (<6% for either group) and not clinically relevant. **Dabrafenib/Trametinib combination:** Study BRA115947 is a NCI sponsored Phase 1 and PK study to evaluate the safety, tolerability and PK of dabrafenib in subjects with severe renal or moderate to severe hepatic impairment. The protocol has been finalised; the final study report is projected to be available by 4Q 2015. This study will inform on the combination treatment strategy in these patients.'	This is considered acceptable.
Safety in patients with moderate to severe hepatic impairment.	'GSK proposes to conduct a study both for trametinib and dabrafenib. **Trametinib:** Study MEK116354 is a Phase 1 and PK study to evaluate the safety, tolerability and PK of trametinib in subjects with hepatic impairment (mild, moderate and severe). The study will be conducted by the National Cancer Institute and a final protocol will be available September	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
	2013, with a projected completed date of June 2015, and final report available by December 2015. **Dabrafenib/Trametinib combination:** Study BRA115947 is a NCI sponsored Phase 1 and PK study to evaluate the safety, tolerability and PK of dabrafenib in subjects with severe renal or moderate to severe hepatic impairment. The protocol has been finalised; the final study report is projected to be available by 4Q 2015. This study will inform on the combination treatment strategy in these patients.'	
Unless sufficient existing data is available, the sponsor should consider conducting a study (or assign this to an existing study) to investigate the safety profile of a combination of trametinib and other agents likely to be co-administered currently or in the future (such as IL-2 or ipilimumab).	'GSK is considering a range of development options for trametinib, in combination with dabrafenib and in combination with other agents. GSK is also developing trametinib or combinations with trametinib in a range of tumour types. GSK only supports the use of trametinib as part of sponsored or supported clinical trials, a compassionate care program or for patients receiving medicinal product in line with an approved indication. GSK-sponsored clinical trials are currently ongoing for combination therapy with other agents as follows: **BRF115984** Phase 1 Study of the BRAF Inhibitor Dabrafenib +/- MEK Inhibitor Trametinib in Combination with Ipilimumab for V600E/K Mutation Positive Metastatic or Unresectable Melanoma) **MEK116833** An Open-Label, Three-Part, Phase I/II Study to Investigate the Safety, PK, PD, and Clinical Activity of the MEK Inhibitor GSK1120212, BRAF Inhibitor GSK2118436 and the anti-EGFR Antibody Panitumumab in Combination in Subjects with BRAF-mutation V600E or V600K Positive Colorectal Cancer Although MEK116833 is being conducted in patients with colorectal cancer and not metastatic melanoma, the safety profile of the combination therapy with panitumumab will still be informative for the latter population.'	This is considered acceptable.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The Chemistry and Biopharmaceutic Summary for ACPM notes:

The highest strength tablet (2 mg trametinib) contains 0.25 mg of DMSO. Formulation of a solvate is unusual, but DMSO toxicity is low (as a manufacturing solvent, residues of up to 50 mg per day are typically allowed). The label claim is the equivalent amount of unsolvated trametinib.

It is also noted that:

Trametinib tablets tend to lose DMSO over time, especially at high temperature and humidity. This adversely affects tablet dissolution. Thus, unusually for a tablet, refrigerated storage is proposed (2-8°C).

Registration was recommended with regard to chemistry, quality control and biopharmaceutic aspects.

Nonclinical

There were no non-clinical (toxicology) objections to registration of either trametinib as monotherapy or trametinib in combination with dabrafenib.

Clinical

The clinical evaluator recommended rejection of the application.

Overview of data

Table 17: Studies relevant to this application

Study ID	Phase	Study drug/s	Population	Endpoints / comments
MEK111054	1	trametinib	Solid tumours, lymphomas	FTIH; dose escalation; anti-tumour activity.
MEK113709	1	trametinib	Solid tumours	Food effect
MEK113708	1	trametinib	Solid tumours	Mass balance
MEK115064	1	trametinib	Solid tumours	Absolute bioavailability
MEK113583	2	trametinib	BRAF mutant melanoma, 2nd line	PK, efficacy, safety.
MEK114267 "METRIC"	3	trametinib versus chemotherapy	BRAF V600E/K mutant advanced melanoma	PK, efficacy, safety. Pivotal for monotherapy.
BRF113220 Part A	1-2	trametinib, dabrafenib[A]	BRAF mutant melanoma	PK / interaction study
BRF113220 Part B	1-2	trametinib, dabrafenib[A]	BRAF mutant melanoma or colorectal cancer	PK, dose escalation
BRF113220 Part C	2	dabrafenib[A] + trametinib versus dabrafenib[A]	BRAF V600E/K mutant advanced melanoma	Pivotal for combination therapy.
BRF113220 Part D	1-2	dabrafenib[B]; dabrafenib[B] + trametinib	BRAF mutant melanoma	PK

A: gelatin capsule; B: HPMC capsule (commercial dabrafenib uses the HPMC capsule)
Some aspects of BRF113220, unrelated to combination therapy, were evaluated in the CER for dabrafenib (PM-2012-02231-3-4).

Pharmacokinetics

ADME

Absorption: Trametinib is quite quickly absorbed (T_{max} 1.5-2 hours). Absolute bioavailability of the 2 mg tablet is 72.3% (four subjects were assessed; individual values were from 45.7-92.8%).

In a single dose study, there was a distinct food effect: with a high fat/calorie meal, C_{max} fell by 70%, but $AUC_{0-\infty}$ fell by only 10%, relative to fasted conditions. Washout was incomplete in this study (seven days) so correction was made for residual concentrations. Food effect with repeat dosing is unknown. The proposed PI advises administration under fasted conditions, consistent with use in the pivotal Phase III Study MEK114267.

Table 18: PK parameters with repeat dosing of 2 mg trametinib

Study	n	Day	Tmax (hr)	Cmax (ng/mL)	AUC(0-24) (ng*hr/mL)	Cτ (ng/mL)
MEK111054 (FTIH)[1]	13	15	1.8 (1.0, 3.0)	22.2 (28)	370 (22)	12.1 (19)
BRF113220 (Combination)[2]	4	15	1.5 (1.0, 2.0)	22.4 (30)	394 (35)	12.4 (42)
BRF113220 (Combination)[2]	12	21	2.0 (1.0, 8.2)	22.6 (36)	351 (34)	10.8 (34)

Abbreviation: FTIH, first time in humans

Data reported as geometric mean (%CVb); tmax reported as median (min, max).

1. Includes loading dose regimens
2. Administered in combination with 150 mg BID of dabrafenib

Inter-subject variability in C_{max}, AUC and C_{trough} was not pronounced. PK was dose-proportional in the range 0.125-4 mg with repeat dosing.

Distribution: IV, trametinib is highly bound to plasma proteins. Partitioning into blood cells varied IV at relevant concentrations: at 1, 10 and 50 ng/mL the blood/plasma ratio was 3.2, 3.4 and 1.1 respectively. In the mass balance study, a ratio of ~3 was stable over 10 days. Volume of distribution after IV micro-dosing was 1060 L, suggesting wide tissue distribution.

Across studies, estimates of T½ varied from around four to 13 days, and estimates of time to steady state varied from 15 to 28 days. The accumulation ratio (steady state/single dose) was 6.0 with 2 mg once daily dosing.

Metabolism: IV studies found trametinib is metabolised via deacetylation to form M5 or via deacetylation plus mono-oxygenation to form M7. M5 can be N-glucuronidated to M6 and (of lesser importance in humans) M7 can be O-glucuronidated to M9. The sponsor states that deacetylation may be mediated by hydrolytic esterases, for example, carboxyl-esterases or amidases.

Metabolite M5 had activity similar to parent trametinib, but there was relatively low exposure after repeat dosing so M5 was considered unlikely to contribute significantly to clinical activity.

Trametinib was characterised as a low hepatic extraction ratio drug, with low IV plasma CL at 3.21 L/hr (~1% of liver blood flow). Elimination is driven by the capacity of metabolising enzymes (not blood flow).

Excretion: In the mass balance study MEK113708 (n=2) total recover of radioactivity over 10 days was low (37%, 48%). Faecal excretion was the major route of elimination (81% and 94% of excreted radioactivity; trametinib, M5 and M7 identified). Urinary excretion accounted for 6% and 19% of excreted dose (trametinib, M5, M7 and M9 identified).

Special populations: Oral clearance (CL/F) was influenced by gender and BW. A PopPK analysis found that males had a 26% higher CL/F than females. Smaller females are predicted to have moderately higher exposure than heavier males; the sponsor does not propose dose adjustment.

There was no formal study of trametinib PK in renal impairment. A PopPK analysis (including n=223 with mild and n=35 with moderate renal impairment) found no relationship between renal function (glomerular filtration rate (GFR)) and trametinib CL/F. There were no data in patients with severe impairment.

There was no formal study of trametinib PK in hepatic impairment. A PopPK analysis (including n=64 with mild hepatic impairment) found no relationship between hepatic function and trametinib CL/F. There were no data in patients with moderate to severe impairment. A dedicated study is being conducted.

Drug-drug interactions – trametinib as victim: The sponsor writes that hydrolytic esterases are not generally associated with a drug interaction risk. This is supported in the medical literature[23]. Trametinib was not an IV substrate of P-gp or BCRP. The potential for other drugs to affect trametinib's PK profile was considered low.

The sponsor writes:

"Following concomitant administration of trametinib and dabrafenib, a CYP3A4 inducer, repeat-dose C_{max} and AUC of trametinib were consistent with the exposure observed in monotherapy, indicating that a CYP3A4 inducer had no effect on trametinib exposure.

Based on the PopPK analysis, a 16% decrease in trametinib oral bioavailability was noted when administered in combination with dabrafenib."

Drug-drug interactions – trametinib as perpetrator: The non-clinical evaluator writes about trametinib's potential to affect other drugs:

The potential for trametinib to affect the PK of other drugs is considered to be low. In IV studies, trametinib was an inhibitor of CYP2C8, CYP2C9 and CYP2C19, and an inducer of CYP3A4. The most potent inhibition was for CYP2C8 (IC50 = 0.34 µM; equivalent to nine times the clinical bound C_{max}). Induction of CYP3A4 had an EC50 of 1.7 µM, equivalent to 40 times the clinical bound C_{max}. Trametinib inhibited OATP1B1, OATP1B3, P-gp and BCRP, the lowest IC50 was 1.1 µM (BCRP), equivalent to 27 times the clinical bound C_{max}; the IC50 in the P-gp assay was 5.5 µM. The unbound plasma concentration of trametinib (unbound fraction 0.03) would be insufficient to affect the PK of other drugs.

Dabrafenib is metabolised by CYP2C8 +/- CYP3A4. Parts A and B of Study BRF113220 examined interaction between the two agents, and produced conflicting results (Part A, which also assayed dabrafenib metabolites, suggested no interaction; Part B suggested on the basis of cross-study comparison that repeat dosing with trametinib results in higher exposure to dabrafenib than is seen with monotherapy). Part D also examined interaction between the agents, although here the HPMC capsule version of dabrafenib was used. Repeat dosing of the combination resulted in dabrafenib C_{max} and AUC higher than dabrafenib monotherapy C_{max} and AUC (16% and 23% higher respectively; neither increase statistically significant). This was consistent with the findings of a PopPK study, showing that combination with trametinib resulted in a decrease in inducible CL of dabrafenib (ratio 0.689); for dabrafenib, inducible CL represented half of total CL/F.

Gelatine versus HPMC capsule for dabrafenib: Study BRF113220 Part C used gelatine capsule dabrafenib. The commercial formulation is HPMC capsule; use of HPMC results in an increase in exposure, relative to gelatine.

Table 19: Ratio for HPMC/gelatine capsules

Dosing (Source)	Ratio for HPMC/gelatin capsules	
	Cmax	AUC(0-τ) or AUC(0-∞)
Single Dose Monotherapy (Study BRF113468)	2.02 (1.42, 2.87)	1.80 (1.32, 2.46)
Repeat Dose Monotherapy (Population PK analysis)	1.66 (NA)	1.42 (NA)
Repeat Dose Combination (Study BRF113220; Parts B and D)	1.51 (1.10, 2.08)	1.10 (0.84, 1.44)
Repeat Dose Combination (Population PK analysis)	1.46 (NA)	1.33 (NA)

AUC(0-τ)=AUC time 0 to the end of the dosing interval (repeat dose); AUC(0-∞)=AUC time 0 to ∞ (single dose)

[23] Fukami and Yokoi, 2012. The emerging role of human esterases. Drug Metab Pharmacokinet. 27 (5): 466-477

Efficacy – monotherapy

Dosage selection: Dosage selection for Phase II and III monotherapy studies was based on results of Study MEK111054. This assessed single doses in the range 0.125-10 mg, and repeat doses in the range 0.125-4 mg once daily. The MTD was 3 mg once daily, but the recommended Phase II dose was 2 mg once daily (based on safety, PD outcomes and clinical activity). For example, 2.5 mg was not clearly more efficacious than 2 mg; the 2 mg dose had a more favourable safety profile.

Study MEK114267 – pivotal: This was a Phase III, randomised, open-label study of trametinib versus chemotherapy in patients with advanced (unresectable Stage IIIC or metastatic) BRAF V600E or V600K mutation-positive melanoma who had received zero or one prior chemotherapies for advanced disease. The clinical data cut-off was 26 October 2011.

Notable exclusions were prior use of any BRAF or MEK inhibitor or ipilimumab in the advanced setting. Patients with a history of brain metastases were only eligible if brain lesions had been treated with surgery or stereotactic radiation (SRS) and if still present, confirmed stable for at least 90 days prior to randomisation.

322 patients were randomised 2:1 to receive trametinib (n=214) or chemotherapy (n=108) as follows:

- Trametinib 2 mg once daily
- EITHER dacarbazine 1000 mg/m^2 q3wk OR paclitaxel 175 mg/m^2 q3wk, IV

Choice of chemotherapy was at the discretion of the investigator, provided the patient had not received the same chemotherapy before. About a third of chemotherapy arm subjects received paclitaxel.

Treatment continued until disease progression, death or withdrawal for any reason. Cross-over was allowed on disease progression.

An allele-specific polymerase chain reaction (PCR) assay was used in screening. This assay could distinguish BRAF V600E and BRAF V600K mutation subtypes.

Demographic characteristics were well balanced across arms (median age 54 yrs; 18% 65-<75 yrs; 4% 75+ yrs), except that the trametinib arm included 56% males while the chemotherapy arm included 49% males.

Baseline characteristics were fairly well balanced (prior chemotherapy for advanced disease in 34%; ECOG 0 in 64%; visceral disease in 79-83%; 3+ sites of disease in 52-57%; BRAF V600E in 86-90%, V600K in 10-14%; history of brain metastases in 2-4%) except that: a smaller fraction of patients in the trametinib arm (32%) had Stage IIIC, IV M1a or IV M1b disease than in the chemotherapy arm (42%); and the median time since first diagnoses of metastatic disease was 7.4 months for trametinib versus 6.6 months for chemotherapy. These differences would not have biased efficacy results in favour of trametinib.

Prior therapy was well balanced across arms; most prior therapy was in the adjuvant setting but about a third of subjects had prior treatment for advanced disease, most often dacarbazine.

Progression-free survival: The primary objective was to establish the superiority of trametinib over chemotherapy with respect to investigator-assessed PFS in patients with BRAF V600E mutation-positive advanced or metastatic melanoma without a history of prior brain metastases.

In patients with V600E mutations and no prior brain metastases, median investigator-assessed PFS was 4.8 months (trametinib, n=178) versus 1.4 months (chemotherapy, n=95). The HR was 0.44 [95% CI 0.31-0.64] in favour of trametinib.

Median investigator-assessed PFS in the ITT population was 4.8 months (trametinib, n=214) versus 1.5 months (chemotherapy, n=108); HR 0.45 (95% 0.33-0.63). Independent review yielded similar outcomes (HR 0.42).

Analysis by choice of chemotherapy in the control arm (dacarbazine or paclitaxel) was not prominent[24]. Prior chemotherapy (0 versus 1) did not have a substantial impact on the PFS HR.

For BRAF inhibitors, efficacy outcomes appear worse in the V600K subgroup (whether this is due to differing efficacy of the agent in this subgroup, or a less favourable clinical phenotype, is unclear). With trametinib monotherapy, PFS outcomes were closer in the V600K group to those in the V600E group than has been seen with, for example, GSK's dabrafenib. For V600E, the PFS HR was 0.47; for V600K, the HR was 0.50.

Overall survival: Survival was reported in two ways.

For efficacy assessment, investigator-assessed Kaplan-Meier estimates of OS used a data cut-off (26 October 2011) allowing median 4.9 months follow-up across both treatment arms of MEK114267.

For safety assessment, a summary of deaths used that cut-off and another used a cut-off of 23 June 2012 (median survival follow-up time for the trametinib arm of MEK114267 of 11.4 months).

For efficacy, as of the clinical cut-off (26 October 2011), 16% of trametinib subjects (35/214) versus 27% of chemotherapy subjects (29/108) had died. At this stage, median OS had not been reached. The HR was 0.54 (95% CI 0.32-0.92) in the ITT population, despite cross-over after progression, noted below. Estimated survival at six months was 81% (trametinib) versus 67% (chemotherapy).

The most noticeable differences in OS in subgroup analysis were for gender (HR 0.39 in favour of trametinib for females, 0.76 for males) and tumour genotype (HR 0.70 in favour of trametinib for V600K patients; six month survival 75% for trametinib versus 68% for chemotherapy for V600K patients; HR 0.52 for V600E, six month OS 82% versus 67%).

For safety, the first cut-off was 26 October 2011. At that point, 34/211 trametinib subjects had died (16%) versus 13/99 chemotherapy subjects (13%). These figures do not include 14 deaths for subjects who crossed over to trametinib; the sponsor asserts that "disease under study was the primary cause of death" in the 14. The disparity between efficacy and safety assessment deaths as of 26 October 2011 is due to several deaths in subjects who did not receive randomised medicine.

The second cut-off was 23 June 2012; 40% of trametinib subjects (84/211) versus 19% of chemotherapy subjects (19/99) had died. These figures do not include 31 deaths for subjects who crossed over to trametinib; the sponsor asserts that most of these deaths were due to disease under study.

Cross-over: Cross-over from the chemotherapy to trametinib was allowed on disease progression; 51 chemotherapy patients (47%) crossed over to receive trametinib. In the ITT population, 21% of trametinib versus 9% of chemotherapy patients received at least one form of anti-cancer therapy after study drug discontinuation (the sponsor believes this imbalance is attributable to cross-over to trametinib as noted earlier).

Given the influence of cross-over, the more unambiguous measure of efficacy is PFS.

Objective response rate: ORR was 22% (trametinib) versus 8% (chemotherapy) (p=0.01), as assessed by the investigator, for the ITT population. As assessed by the

[24] The FDA summary review states that FDA analysis found similar outcomes for DTIC and paclitaxel patients.

independent panel, the difference remained (19% versus 5%, (p=0.0029)). There was also more stable disease in the trametinib arm than the chemotherapy arm.

For patients with V600K mutation (n=40), the ORR for trametinib (n=29) was 10%, but for chemotherapy (n=11) was 18%. However, stable disease was recorded in 76% versus 18% respectively, so that there was actually less progression in the V600K group given trametinib (10%) than in the V600E group given trametinib (19%).

Quality of life: Health outcomes were assessed at baseline and throughout the study using EORTC QLC-C30 (high functionality scale score = better function; high symptom scale = worse symptom) and EQ-5D (perceived level of problem). In the primary efficacy population, global health status was slightly higher at baseline in the chemotherapy arm (mean 63.4 for trametinib, 68.7 for chemotherapy, with emotional function the main driver of this difference). Symptoms were slightly worse at baseline for trametinib (for example, fatigue, 32.6 versus 28.8; dyspnoea 20.1 versus 15.0). Changes from baseline tended to favour trametinib; although the most pronounced difference was in diarrhoea, favouring chemotherapy. Clinical significance of the changes identified is difficult to assess. The improvement in pain-related quality of life (QoL) for trametinib was consistent in the EQ-5D[25] analysis.

Efficacy following cross-over to trametinib: Median PFS on trametinib was 2.6 months for the cross-over population of 51; ORR was 8%.

Study MEK113583 – supportive

This was a Phase II, single arm, open label study of trametinib (2 mg OD) in 97 patients with BRAF mutation (V600E/K/D) positive, metastatic melanoma. The clinical data cut-off was 25 July 2011, at which time median follow-up was 10.4 months.

Patients had received prior treatment for advanced disease; ECOG performance was to be 0-1. In Cohort A (n=40), patients had received prior dabrafenib (with or without other therapy). In Cohort B (n=57), patients had received prior chemotherapy and/or immunotherapy (without prior BRAF inhibition). A key exclusion was presence of brain metastases (unless previously treated and stable for at least eight weeks). Treatment was continued until disease progression, death or withdrawal.

Mean age was 54.7 years (27% were 65+ years of age); 70% were male; 63% had ECOG performance status (PS) 0. Median days from initial diagnosis to dosing were 1024 (Cohort A) and 922 (Cohort B). More than 73% had stage M1c disease. 13% in Cohort A and 21% in Cohort B had prior brain metastases; 70% and 54% respectively had 3+ disease sites. 81% had V600E and 12% had V600K; no-one had V600D. There was extensive prior treatment of advanced disease. In Cohort A, 3/40 stopped BRAF inhibition due to toxicity but in all others the reason was disease progression.

In Cohort A, there were no responses to therapy and PFS was 1.8 months; Cohort A was terminated due to futility.

In Cohort B, ORR was 25% (26% in V600E; 0% in V600K); stable disease was seen in a further 51% (52% in V600E; 63% in V600K); median PFS was 4 months (4.6 months in V600E; 3.7 months in V600K). Results in patients with brain metastases were worse than in others; for example, median PFS was 3.0 months versus 4.6 months respectively. Survival at 12 months was estimated to be 50% overall, but data were immature.

Study MEK111054 – supportive

This was a Phase I, single arm, open label study in patients with a solid tumour or lymphoma unresponsive to standard therapies. Efficacy was analysed for dosing at 2-2.5

[25] The EuroQual – 5 dimensions (EQ-5D) descriptive system comprises 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

mg OD. There were 206 patients; 81 had melanoma; 30/81 had BRAF mutation-positive melanoma with no prior BRAF inhibitor therapy. There were also 16 subjects with ocular melanoma. The confirmed RR in the 30 BRAF mutation-positive patients with no prior BRAF inhibition was 33%; median PFS was 5.7 months. In wild-type melanoma, ORR was 10% and PFS was 2.0 months. No responses were seen in ocular disease.

Efficacy – combination therapy: The sponsor describes the submission to approve combination therapy as "early" but based on "compelling" data from BRF113220. Two Phase III studies are ongoing:

- MEK115306, n~340, combination therapy versus dabrafenib, results due in the third quarter of 2013.[26]
- MEK116513, n~694, combination therapy versus vemurafenib, results due in the second quarter of 2014.

Dosage selection: Dabrafenib as monotherapy in this setting has a recommended dose of 150 mg twice daily. The proposed trametinib monotherapy dose is 2 mg once daily.

The pivotal study for combination therapy, BRF113220 Part C, allowed assessment of 'dabrafenib 150 mg twice daily + trametinib 1 mg daily 'versus' dabrafenib 150 mg twice daily + trametinib 2 mg daily'. There were discernible differences in efficacy outcomes.

The sponsor notes also an increase in confirmed RR with higher trametinib average exposure (>10 ng/mL).

Study BRF113220 Part C – pivotal

This was a Phase II, open label, randomised study in 162 BRAF inhibitor-naïve patients with advanced BRAF V600 mutation-positive melanoma. The data cut-off was 31 May 2012; an interim analysis was presented. Median follow-up was 14 months. Tumour genotyping (by allele-specific PCR) distinguished V600E and V600K mutations; no other mutations were allowed. Randomisation was into three arms; each had 54 subjects:

- Dabrafenib 150 mg twice daily + trametinib 2 mg (150/2)
- Dabrafenib 150 mg twice daily + trametinib 1 mg (150/1)
- Dabrafenib monotherapy 150 mg twice daily

Demographics and baseline characteristics were reasonably balanced between the 150/2 arm and the monotherapy arm. However, mean age was 55.9 years in the 150/2 arm, versus 51.8 years in the monotherapy arm; 37% versus 46% (respectively) were female; and there were 3 plus sites of disease in 52% versus 63%. ECOG PS was 0 in 63-65%, otherwise 1; V600E was seen in 83-87%; stage at screening was IIIC/M1a/M1b in 30-31%; and there was a history of brain metastases in 4-7%. 78% (150/2) versus 87% (monotherapy) were treatment naïve in the advanced melanoma setting.

Progression-free survival: As assessed by the investigator, median PFS was 9.4 months in the 150/2 arm, 9.2 months in the 150/1 arm and 5.8 months for dabrafenib monotherapy.

The estimated PFS at 12 months was 41% for 150/2 combination versus 26% for the 150/1 combination versus 9% for dabrafenib monotherapy.

In the comparison of 150/2 versus dabrafenib monotherapy, the HR was 0.39 [95% CI 0.25-0.62] in favour of 150/2 combination therapy.

[26] For information, GSK has agreed to provide the EU CHMP a high level data report, which the company predicts to be available in November 2013.

The BIRC's assessment resulted in some differences, attributed by the sponsor to imbalance in informative censoring, as follows:

- Median PFS was 9.2 months for 150/2, 8.3 months for 150/1 and 7.3 months for monotherapy;
- The HR (PFS; 150/2 versus monotherapy) was 0.54 (95% CI 0.32-0.91);

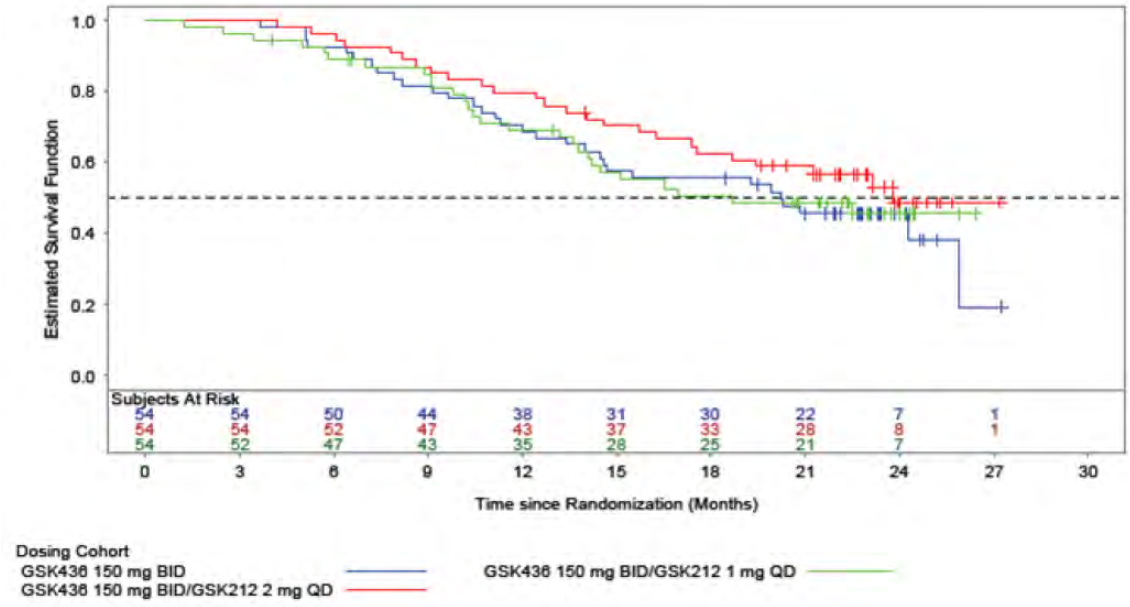
In the 43 subjects who crossed over from the monotherapy arm to the 150/2 arm, median PFS in the cross-over phase was 3.6 months (best confirmed ORR 9%).

Unlike the situation with dabrafenib and trametinib monotherapies, with 150/2 similar PFS benefit was seen for V600E and V600K. For V600E, median PFS was 10 months in the 150/2 arm (n=47) versus 6.5 months for dabrafenib (n=45). For V600K, median PFS was 9.3 months for 150/2 (n=7) versus 4.3 months for dabrafenib (n=9). Sample size for V600K was limited, but the analysis was able to confirm the lower response in V600K for dabrafenib seen in the dabrafenib application.

Overall survival: Median OS had not been reached in any arm, based on median follow-up of 14 months. The Kaplan-Meier estimate of OS at 12 months was 79% for the 150/2 combination arm, 68% for the 150/1 arm and 70% for the monotherapy arm. For these OS data, all death following cross-over was included in the monotherapy group. 43/54 monotherapy arm subjects crossed over to 150/2 on disease progression. The HR was 0.67 (95% CI 0.34-1.34, ns) favouring the 150/2 over the monotherapy arm.

Updated OS analysis was conducted with a data cut-off of 29 March 2013. At the time of updated OS analysis, median follow-up time was 24 months, compared to 14 months at time of primary analysis of PFS. At this cut-off, median OS was 20.2 months in the dabrafenib arm, 18.7 months in the 150/1 arm and 23.8 months in the 150/2 arm. The HR was 0.73 (95% CI 0.43-1.24) in favour of 150/2 over dabrafenib. This was despite 83% of the dabrafenib monotherapy arm crossing over at time of progression. The KM curve for OS based on updated results is indicated in Table 20.

Table 20: The Kaplan-Meier curve for overall survival



Objective response rate: Objective response (CR+PR) as assessed by the investigator was 76% for the 150/2 arm versus 54% for dabrafenib. Median duration of response was 10.5 months for the 150/2 arm, versus 5.6 months for the dabrafenib monotherapy arm.

ORR as assessed by the BIRC was 61% for 150/2 combination therapy versus 46% for dabrafenib monotherapy. Median duration of response was 7.6 months for both the 150/2 arm and the dabrafenib monotherapy arm.

In the V600E subgroup, ORR in the 150/2 arm was 77%, versus 58% for dabrafenib. In the V600K subgroup, ORR in the 150/2 arm was 71% (5/7) versus 33% for dabrafenib (3/9).

Within the cross-over cohort (n=43), PR was only seen in subjects who had objective responses to dabrafenib (that is, in 4/24).

Quality of life: This was apparently not assessed.

Study BRF113220 Part B – supportive

The highest three cohorts in this part of the study, namely 150/1, 150/1.5 and 150/2 (n=24; median follow-up 15.4 months), were expanded to a maximum of 25 subjects. Several expansion cohorts were studied, including one of patients with BRAF V600 mutation-positive melanoma who had disease progression following prior treatment with a BRAF inhibitor. Patients in Part B had more advanced disease than those in Parts C or D.

In the 24 patients given 150/2 combination therapy, investigator-assessed median PFS was 10.8 months (similar to the median of 9.4 months in Part C). Investigator-assessed ORR was 63% (lower than the 76% for Part C).

In 26 BRAF inhibitor pre-treated subjects who were given combination therapy in Part B, there was limited clinical activity (PFS 3.6 months; 15% ORR).

Study BRF113220 Part D – supportive

39 patients received dabrafenib 150 mg twice daily + trametinib 2 mg once daily. The data cut-off was 25 September 2012. Median follow-up was 7.7 months. PFS data were immature. Investigator-assessed ORR was 67% (less than the 76% for Part C).

Safety

Exposure: As of 23 June 2012, 1749 subjects had received ≥ 1 dose of trametinib including 1185 subjects who had received trametinib 2 mg.

The sponsor compared three safety populations: trametinib monotherapy (n=329 from MEK114267; MEK113583; MEK111054), dabrafenib monotherapy (n=586 across five studies) and combination therapy (primary comparison used the 150/2 arm within Part C of BRF113220, n=55[27]; a total of 202 subjects were in the pooled 150/2 safety set).

In the trametinib monotherapy population, median duration of exposure was more than double that of chemotherapy (4.8 versus 2 months). Duration of exposure was longer in the 150/2 arm of Part C than for trametinib or dabrafenib.

[27] One subject randomised to monotherapy inadvertently received 150/2 therapy and was included in the safety set for analysis.

Table 21: Duration of exposure in monotherapy and combination therapy populations

	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
Dabrafenib - Time on Study Treatment (Months)					
Median (Min – Max)	10.94 (1.87-17.28)	6.55 (0.03-19.65)	--	5.47 (0.07-22.60)	6.08 (1.81-15.21)
Trametinib - Time on Study Treatment (Months)					
Median (Min – Max)	10.91 (1.77-17.28)	6.41 (0.03-19.65)	3.84 (0.0-24.5)	--	--

Data Source: m2.7.4 SCS Section 1.5

Overview of adverse events: In integrated trametinib monotherapy studies, a wide spectrum of AEs was reported, and AEs were commonly severe or life-threatening. Despite this, 'only' 10% of patients required drug discontinuation; instead, dose interruption or reduction was often employed. 92% of patients could continue trametinib until disease progression.

In the Part C 150/2 combination therapy arm, as with trametinib alone, a large fraction of subjects (9%) had to discontinue treatment due to AEs; both dose interruption and dose reduction were employed more than for trametinib alone, suggesting combination therapy may be more difficult to tolerate.

Most AEs were more frequent in the Part C 150/2 arm than in the monotherapy safety populations, but there were exceptions such as rash, diarrhoea and peripheral oedema.

Deaths and other serious AEs: In trametinib monotherapy studies, five patients (2%) had fatal AEs – GI fistula; hepatic failure and renal failure; myocardial infarction; renal failure; and 'death'. In one case (renal failure 10 days after the first dose), a potential link with trametinib was made, via gastroenteritis leading to dehydration. 2% of chemotherapy patients also had fatal AEs.

In the Part C 150/2 arm, 3/54 (5%) had fatal AEs. In the pooled 150/2 population, seven patients (3%) had fatal AEs (5/7 were ≥ 65 years of age, so that Grade 5 events occurred in 12% in this age group). One of these AEs was considered drug-related (ventricular arrhythmia in a subject with a history of hypertension).

In the trametinib monotherapy studies, 22% of patients experienced a SAE (in the pivotal study, 24% for trametinib versus 20% for chemotherapy); more common SAEs were cellulitis (3%), pulmonary embolism (2%), anaemia, dyspnoea, pneumonitis, vomiting, dehydration and erysipelas.

In the Part C 150/2 arm, 62% had an SAE. Pyrexia (25%) and chills (18%) were the most common SAEs by far, then dehydration, decreased ejection fraction, pneumonia, pulmonary embolism, acute renal failure and SCC (all reported in 2/54 subjects). 11% of patients in the Part C 150/2 arm required hospitalisation for pyrexia (versus one out of 54 in the dabrafenib monotherapy group).

Common AEs: In trametinib monotherapy studies, more common AEs were rash (58%), diarrhoea (49%), fatigue (33%), peripheral oedema (33%), nausea (30%), dermatitis acneiform (22%) and vomiting (20%). In MEK114267, trametinib had a quite different safety profile than chemotherapy, with a much higher incidence of rash, diarrhoea, peripheral oedema, dermatitis acneiform, dry skin, pruritus, hypertension and paronychia, but a decreased incidence of nausea.

In trametinib monotherapy studies, Grade 3-4 AEs were in total more common than Grade 1-2 AEs; more common Grade 3-4 AEs were hypertension and rash. There were four Grade 4 pulmonary embolisms for trametinib.

In the monotherapy studies, more common drug-related AEs were rash, diarrhoea, fatigue, dermatitis, peripheral oedema, nausea, dry skin, pruritus, alopecia and vomiting.

In the Part C 150/2 arm, AEs in > 30% were pyrexia (71%), chills (58%), fatigue (53%), nausea (44%), vomiting (40%) and diarrhoea (36%). These were also the more common drug-related AEs. Other common AEs (seen in >20%) were cough, headache, peripheral oedema, arthralgia, rash, night sweats, constipation, decreased appetite and myalgia.

In the Part C 150/2 arm, Grade 3-4 AEs were reported in 64% (versus 43% for dabrafenib). In the Part C 150/2 arm, neutropenia (6/55, 10%) and hyponatraemia (4/55, 7%) were common severe or life-threatening AEs.

AEs leading to discontinuation or dose modification: In the pivotal monotherapy study MEK114267, discontinuation due to AEs was seen in 12% (trametinib) versus 9% (chemotherapy). Pneumonitis (n=4) and ALT elevation (n=3) were AEs leading to permanent discontinuation in multiple patients. Discontinuation was more frequent in older age brackets. There were more dose reductions or delays in the trametinib arm than the chemotherapy arm (but dosing regimens were quite different).

In the monotherapy studies, 26% of trametinib patients had dose reductions due to AEs (in the pivotal study, 32% for trametinib versus 10% for chemotherapy) and 36% had dose interruptions due to AEs (in the pivotal study, 38% versus 24% respectively). Common AEs leading to dose reduction were rash, decreased ejection fraction and dermatitis.

In the Part C 150/2 arm, 5 patients (9%) discontinued study drug permanently. In two patients the AE was pyrexia. (In the dabrafenib safety set, 3% had to discontinue).

In the Part C 150/2 arm, 49% of subjects had dose reductions (of either or both drugs, though dabrafenib was more often involved) and 67% had dose interruptions (often due to pyrexia or chills). Most subjects with dose reductions re-escalated.

Specific toxicities: The sponsor identified toxicities characteristic of trametinib. Some were magnified in the combination arm (for example, pyrexia, renal failure and ocular events), some were unchanged (for example, cardiac events) and some were less prominent (for example, hyperproliferative skin lesions, and hypertension).

Skin toxicity including rash: BRAF inhibitors are associated with cutaneous SCCs/KAs. In trametinib monotherapy studies, there were no reports of SCC or KA, suggesting that the paradoxical activation of the RAS/RAF/MAPK pathway described for small molecule BRAF inhibitors does not occur with trametinib.

In the Part C 150/2 arm, incidence of hyperkeratosis and skin papilloma was lower than in the dabrafenib safety population. Also, Grade 3 SCC – in 7% of the dabrafenib safety population – was reported in 4% of patients in the combination group (and median time to first occurrence was longer than with BRAF inhibitor monotherapy).

Trametinib was associated with skin toxicity (in the pivotal study, 88% for trametinib versus 14% for chemotherapy); rash and dermatitis acneiform were very common, and rash was severe in 8% (one patient had life-threatening rash which resolved on stopping therapy). Events often occurred within the first 28 days of treatment; median duration was 72 days, that is, skin toxicity could be persistent, but 89% of skin-related events did not require dose modification.

Care guidelines like those used for epidermal growth factor receptor (EGFR) inhibitors were implemented to manage rash.

In the Part C 150/2 arm, incidence of rash was lower than in the trametinib population. Grade 3 rash was seen in 7% of the trametinib safety population but was not reported in the Part C 150/2 arm.

Palmar-plantar erythrodysaesthesia was a specific AE observed in the dabrafenib safety population (14% incidence); it was reported in 7% of the Part C 150/2 arm.

Diarrhoea: In integrated trametinib monotherapy studies, diarrhoea occurred in 49% of subjects. In 3% the AE was severe; there were no life-threatening events. Diarrhoea most often occurred within the first 14 days; in about half of subjects, it was prolonged (>10 days). Detailed management guidelines for diarrhoea were in place in MEK113583 and MEK114267.

In the Part C 150/2 arm, incidence of diarrhoea was lower than in the trametinib safety population.

Ocular AEs and visual impairment: RVO and central serous retinopathy are reported with MEK inhibitors. Ocular AEs were common in integrated trametinib monotherapy studies; for example, blurred vision (6%) or dry eyes (3%). Three patients experienced chorioretinopathy; two of the three AEs were severe. There was one case of Grade 3 RVO.

In the total trametinib study programme, 14 cases of central serous retinopathy have been observed; not all patients ceased therapy. There were two cases of papilloedema, both confounded by brain metastases, and three cases of optic nerve oedema. There were four SAEs of RVO, treated successfully in two patients with anti-vascular endothelial growth factor (VEGF) therapy (trametinib was ceased).

In the Part C 150/2 arm, ocular AEs were reported in 25% (versus 8% for the dabrafenib safety population and 13% for the trametinib safety population); common AEs were blurred vision, dry eye and visual impairment. Incidence of uveitis, iritis or iridocyclitis was 2% in patients on combination treatment in BRF113220, versus 1% with dabrafenib. Severity of ocular AEs was increased and median time to resolution was longer in the combination arm.

Hepatotoxicity: In the integrated monotherapy studies, 39 patients (12%) had 82 hepatic AEs, typically low grade transaminitis. In the pivotal study, the incidence was 11% (trametinib) versus 5% (chemotherapy). Nine patients had Grade 3 hepatic events; two patients had Grade 4 AEs. There were no cases conforming to 'Hy's Law'.

Hepatic events were more common in the Part C 150/2 arm (11%) than the monotherapy arm (2%); transaminitis was the most common event but 3/54 '150/1' subjects had hyperbilirubinaemia. Given the small sample size in Part C, there is a possibility that the dabrafenib/trametinib combination may have considerable hepatotoxicity.

Cardiotoxicity including sudden death and left ventricular (LV) dysfunction: Study MEK111054 analysed the relationship between trametinib exposure and QTc in 50 subjects. There was no clinically significant QTc-prolonging effect at the mean Cmax observed with 2 mg once daily. In the integrated monotherapy dataset, eight patients developed QTc prolongation (change from baseline >60 msec), and n=5 had QTc prolongation to above 500 msec. Across the trametinib programme, there have been several drug-related fatal AEs consistent with ventricular arrhythmia. A study of trametinib's effect on cardiac repolarisation is ongoing (MEK114655), as is one for dabrafenib (BRF113773); neither study seems to assess combination therapy.

Cardiomyopathy is an important side effect of trametinib. Cardiac-related events such as decreased ejection fraction, LV dysfunction and cardiac failure were reported in 9% (n=31) of the integrated monotherapy population (8% in the pivotal study's trametinib arm, 0% in the chemotherapy arm). Eight subjects had severe events (four with decreased ejection fraction, three with LV dysfunction and one with cardiac failure). In 5/31, treatment was discontinued.

Across the entire trametinib programme, there have been seven fatal cardiac AEs, three of which were considered drug-related (cardiogenic shock, cardiac arrest and ventricular arrhythmia – all in subjects using trametinib in combination with a chemotherapy agent).

Hypertension has been reported with MEK inhibitors. In the integrated monotherapy studies, hypertension was seen in 15% of subjects; 9% of cases were 'severe' although there were no SAEs or AEs of hypertension resulting in permanent discontinuation. Onset was generally after ~14 days. There was no specific BP monitoring programme so it is possible these outcomes underestimate incidence; conversely, there was no specific management programme.

In the Part C 150/2 arm, the incidence of Grade 3 hypertension was lower than in the trametinib population (2% versus 9%).

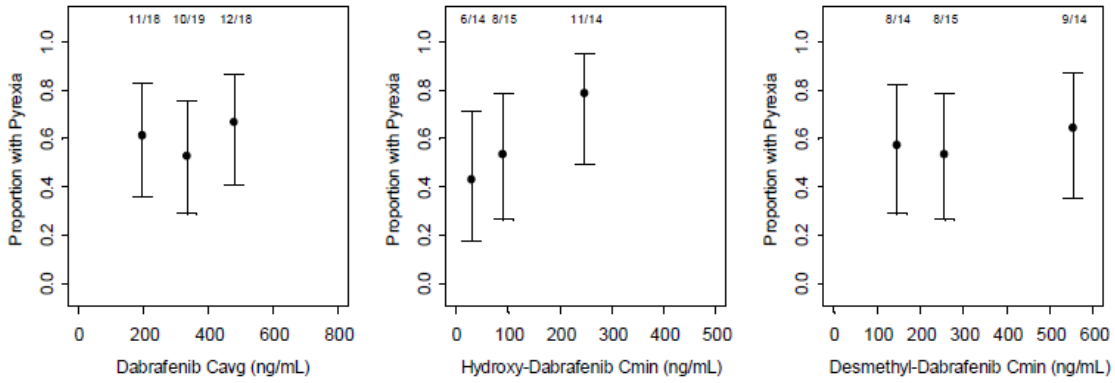
Pneumonitis: In integrated monotherapy studies, five patients (2%) reported pneumonitis as an SAE. In all cases the AE resolved upon stopping trametinib and starting symptomatic treatment.

Pyrexia: Incidence and severity of pyrexia (and related events) were the most significant safety concerns in relation to combination therapy, at least relative to monotherapy.

Pyrexia and related events are common with BRAF inhibitors, for example, the incidence is 33% for dabrafenib monotherapy. Combination therapy resulted in a dramatically increased incidence, 76%. A third of patients experienced ≥3 events. Management with steroids (often for months) or dose modification was often required; 5% of patients in the Part C 150/2 arm permanently discontinued due to pyrexia. Complications or accompanying AEs included hypotension, dehydration, severe chills and renal failure; the frequency of such events was also higher with combination treatment than with dabrafenib.

A trend toward higher rates of pyrexia was noted with higher hydroxydabrafenib concentrations in BRF113220 Part C:

Table 22: Rates of pyrexia with hydroxydabrafenib concentrations



CYP2C8 and CYP3A4 are implicated in transformation to hydroxyl-dabrafenib.

The mechanism of pyrexia/systemic inflammatory response remains unclear.

Renal impairment: In Part C 150/2, 4/54 (7%) experienced renal failure – a higher incidence than in either monotherapy safety population (≤2%). Acute renal failure was often seen in the context of pyrexia and dehydration.

Secondary malignancies: In the monotherapy studies, there were no reports of secondary malignancies causally related to trametinib. In BRF113220, there were no AEs of new primary melanomas in subjects on combination therapy. In 365 combination therapy subjects in BRF113220, there were four cases of treatment-emergent malignancies; in at least one subject (#2918; colorectal cancer) a mutation in RAS was

defined. The other subjects had: glioblastoma, pancreatic cancer and renal cell cancer (the last present at baseline). Overall, there was no clear evidence of any increase in secondary malignancies with combination therapy relative to dabrafenib.

Peripheral oedema: This has been reported in previous studies of MEK inhibitors. In integrated trametinib studies, 43% reported oedema; eight AEs were severe. In the Part C 150/2 arm, peripheral oedema was less common.

Laboratory abnormalities: In integrated monotherapy studies, anaemia was reported in 40% (including 4% with Grade 3); neutropenia was reported in 14% (with no Grade 3 AEs); thrombocytopenia was reported in 19% (there was one Grade 4 episode). Grade 3-4 neutropenia was more frequent in the Part C 150/2 arm than in either monotherapy population. In Part C of BRF113220, a 150/1 patient died of haemorrhage on a background of low platelets. Hyponatraemia was prominent in the combination therapy arms of BRF113220 Part C.

Other: Fatigue, nausea and vomiting were more frequent in the Part C 150/2 arm than in the trametinib safety population.

The non-clinical evaluator noted increased serum phosphorus levels, producing mineralisation in organs at trametinib levels below the equivalent clinical dose level; the effect was not obvious in humans.

The non-clinical evaluator also noted testicular toxicity in dabrafenib/ trametinib combination studies, and a potential for impaired female fertility with trametinib. Further, Pregnancy Category D is proposed.

Risk management plan

The RMP proposed by the sponsor was considered generally acceptable by the TGA's Office of Product Review (OPR). The RMP evaluator recommends that:

- Pharmacovigilance concerning use in patients with heart failure be strengthened (this issue does not appear to preclude registration and will be left for the RMP Evaluation section to resolve with the sponsor).
- Clinical monitoring requirements (skin/cardiac/ocular/pulmonary) be better communicated in the PI (these aspects have been considered in this overview).

The following RMP version will be referenced in a condition of registration:

EU Risk Management Plan (EU-RMP) Version 0.0 (dated 31/01/2013, DLP 25/09/2012) with Australian Specific Annex (ASA) Version 1 (undated).

Delegate considerations

Efficacy – monotherapy

Given the choice of control regimen in the trametinib monotherapy pivotal trial, it is relevant that dacarbazine is indicated for this use (paclitaxel is not, but is included as an active agent in National Comprehensive Cancer Network (NCCN) guidelines). The sponsor writes:

> "Subjects were enrolled in MEK114267 from November 2010 until June 2011. During study conduct, the active, novel agents, ipilimumab and vemurafenib, were not yet approved by regulatory agencies and thus, systemic chemotherapy was considered the standard of care in unresectable or metastatic melanoma."

PFS was the primary endpoint finally settled on in MEK114267. This is a reasonable decision given that OS outcomes in the chemotherapy arm would likely be confounded by use of subsequent active therapies. Prolonged PFS is considered to be of benefit to a given patient, especially when coupled with evidence that QoL is not reduced and that OS may be improved.

The clinical evaluator considered further assessment is required in relation to BRAF V600K mutation-positive patients to be confident that the benefits for these patients are comparable to those with BRAF V600E mutation-positive disease.

There is no absolute need to establish that benefit is similar for V600E and V600K. The benchmark should be whether benefit/risk in V600K is better with trametinib than that for established therapies.

Current evidence suggests efficacy of trametinib monotherapy is lower in V600K than in V600E; the difference appears less than with, for example, dabrafenib. An advantage of trametinib over chemotherapy is likely. The higher ORR for chemotherapy than trametinib in the pivotal monotherapy study's V600K subset (18% versus 10%) is offset by results for stable disease, PFS and OS.

No clinical trial data inform efficacy in other BRAF mutations, but sufficient numbers of patients with such rare mutations will be difficult to achieve in trials. The safety profile should not differ across different mutation types, but efficacy may vary. It is incorrect to assume that pre-clinical demonstration of efficacy in rarer mutation subtypes is well correlated with clinical efficacy.

Considering the approach to this issue taken for both vemurafenib and dabrafenib, I support the less restrictive V600 indication, but the ACPM's advice is requested.

Results in BRAF inhibitor-treated populations demonstrate limited activity with the combination or trametinib monotherapy when administered sequentially after a BRAF inhibitor.

Efficacy – combination therapy

The comparator in BRF113220 Part C was dabrafenib (gelatine capsule). Gelatine capsules results in lower exposure, which might bias towards lower dabrafenib efficacy (relative to efficacy where HPMC capsules are used). Gelatine capsules were used in both arms of Part C, so the effect of lower exposure is difficult to assess. It might magnify the additional benefit of trametinib in combination therapy.

A key issue is that relatively few people in the proposed target population have been studied, and follow-up is not long (so some efficacy endpoints are not 'mature').

Safety – monotherapy

Patients treated with trametinib had a high incidence of severe or life-threatening AEs (Grade 3-4 AEs outweighed Grade 1-2 AEs). Permanent discontinuation was required in 10% (higher than the rate seen in combination therapy [9%]; and in the pivotal study, higher than seen with chemotherapy [12% versus 9%]). The monotherapy cohort was not large (n=329) so is unlikely to have detected uncommon (for example, <1% frequency) SAEs. This is offset by the life-threatening nature of advanced melanoma; but even with observed results, trametinib monotherapy has clear toxicity.

Safety – combination therapy

Tolerability of the combination regimen is lower relative to monotherapies, requiring more frequent dose modification to manage AEs.

The median time on treatment for subjects in BRF113220 Part B (gelatine dabrafenib) was 11.5 months, Part C (gelatine dabrafenib) was 10.9 months and Part D (HPMC dabrafenib) was 6.2 months. This and the small sample sizes involved make it difficult to rule out any increase in AEs with HPMC dabrafenib due to the increased systemic exposure associated with this HPMC capsule form. Skin rash and diarrhoea were AEs reported as generally starting within a month of treatment. For both these AEs, the incidence in 39 subjects given HPMC dabrafenib was not especially greater than the incidence in 79 subjects given gelatine dabrafenib (BRF113220 Part D versus Parts B+C).

In the sponsor's safety update, patients in Part D of BRF113220 had a longer duration of drug exposure (now 8.4 months, from the 6.2 months reported above, that is, closer to the duration of exposure in Part C at 10.9 months). In this update, the major difference in AEs observed between Part C and Part D was in drug-related SAEs (45% versus 64% respectively), such as pyrexia, chills and cytokine release syndrome. Other relevant AE groupings (for example, AEs leading to discontinuation) showed no particular differences across Parts.

Benefit/risk – monotherapy

Selection of therapy is guided by efficacy and safety. The standard of care in advanced BRAF mutant melanoma is not chemotherapy now, but vemurafenib or dabrafenib. NCCN version 2014.1 states that the principle indication for primary treatment of BRAF mutated metastatic melanoma with trametinib is intolerance to BRAF inhibitors. This possibly reflects the toxicity of trametinib and the absence of a clear efficacy advantage over BRAF inhibitors.

The Delegate considers that there is a positive benefit/risk balance for trametinib monotherapy in cases where BRAF inhibition cannot be used (but not where BRAF inhibition has failed). This is because the toxicity of trametinib monotherapy is distinctly greater than for the BRAF inhibitors (see 'Safety – monotherapy' above), and there is no apparent efficacy advantage over those agents. One concern is that cross-intolerance between dabrafenib and trametinib is not well studied.

Benefit/risk – combination therapy

The sponsor claims that combination therapy results in more inhibition of the MAPK pathway, leading to a more pronounced initial response to therapy and prevention or delayed emergence of acquired resistance through reactivation of the MAPK pathway. The sponsor also notes that data support early combination treatment.

The Delegate considers that despite the limitations in the dataset provided, there are sufficient data to support the approval of the 150/2 combination. Efficacy is clearly better with the 150/2 combination that with dabrafenib, which itself is clearly better than dacarbazine. This gain in efficacy will not be experienced by everyone because the toxicity of the 150/2 combination is such that around 10-15% of subjects will have to discontinue use or even experience fatal AEs. Many other subjects will have to endure significant drug-induced AEs, and dose modification will be required in the majority. It is not clear that QoL will be improved in subjects on the 150/2 combination, but at least for trametinib monotherapy most aspects of health related quality of life improved relative to chemotherapy, despite trametinib's own significant toxicity profile.

Given the toxicity evident with combination therapy, benefit/risk may be optimised by restricting use to patients with better performance status. The pivotal study restricted use to patients with ECOG PS 0-1. Also, key safety outcomes were worse in older patients, for example, fatal AEs became far more common in older subjects.

One concern is that benefit seen with 150/2 combination therapy in BRF113220 Part C will not be seen in follow-up studies. Part C was limited in size and follow-up (although updated OS data provide some reassurance that initial efficacy outcomes were valid). There were very limited supporting data for the 150/2 combination, although the data offered in BRF113220 Parts B and D did support results in Part C. The effect size in Part C is considerable and this offsets the sample size limitations of the study, to the extent that differences in PFS between 150/2 combination and dabrafenib reached statistical significance. While the same cannot be said for OS differences, these were confounded by cross-over.

Proposed action

The Delegate supported the following modified indication:

> *Mekinist as a monotherapy is indicated for the treatment of patients with BRAFV600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma who are intolerant of BRAF inhibitors or for whom BRAF inhibitors are contraindicated.*
>
> *Mekinist as monotherapy has not demonstrated clinical activity in patients who have progressed on BRAF inhibitor therapy (see CLINICAL TRIALS).*
>
> *Mekinist in combination with dabrafenib is indicated for the treatment of patients less than 65 years of age, with ECOG performance status 0-1 and with BRAFV600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma.*

A caveat concerning combination use in patients who have progressed on prior BRAF inhibitors or trametinib is not needed: results after progression on dabrafenib were not abysmal (for example, BRF113220: cross-over phase of Part C; Part B).

Restrictions built into the combination therapy indication can be lifted if Phase III data suggest utility in older subjects or those with worse performance status.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. For trametinib, efficacy appears comparable to that seen with BRAF inhibitors (perhaps better for V600K disease), but toxicity appears worse. In what advanced melanoma population (if any) does trametinib monotherapy have a positive benefit/risk balance?
2. For combination therapy, evidence is based on a limited number of trials, with limited sample size and follow-up. Phase III studies are progressing. Are efficacy and safety data reliable based on the submitted data?
3. If the committee considers efficacy and safety data reliable for combination therapy, in what population of advanced melanoma patients (if any) is there a positive benefit/risk balance for combination therapy?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Executive summary

The Delegate recommended registration of Mekinist as a monotherapy and in combination with dabrafenib for the treatment of patients with V600 mutation-positive metastatic melanoma.

Trametinib monotherapy was approved by the FDA (29 May 2013) and dabrafenib monotherapy by the TGA (21 August 2013) for a similar patient group.

Monotherapy

Trametinib demonstrated superiority over chemotherapy in the primary efficacy (PE) endpoint of PFS in pivotal Phase III Study MEK114267. PFS is an acceptable endpoint as a measure of efficacy in this patient population (compared to OS) to the Delegate given the "influence of cross-over" on disease progression in the trial designs based on ethical considerations.

Recent updated OS data (data cut-off 20 May 2013) confirm that survival is comparable for all BRAF V600 mutation-positive metastatic melanoma monotherapy treatments (trametinib/dabrafenib/vemurafenib).

Clinical benefit has been demonstrated for trametinib in patients with the two key distinct genotypes: BRAFV600E and BRAFV600K in studies MEK114267 and MEK113583.

Class-specific AEs for trametinib are clinically manageable.

Trametinib's distinct safety profile, compared to BRAF inhibitors, justifies a broad indication to allow individual physicians and patients the opportunity to select an active drug aligned to the individual patient's situation. Therefore, GSK is seeking registration for the following monotherapy indication:

> *Mekinist as a monotherapy is indicated for the treatment of patients with BRAFV600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma.*
>
> *Mekinist as monotherapy has not demonstrated clinical activity in patients who have progressed on BRAF inhibitor therapy (see Clinical Trials).*

Combination

The combination of dabrafenib/trametinib (150 mg dabrafenib twice daily /2 mg trametinib once daily (150/2) demonstrates compelling clinical results when compared to dabrafenib monotherapy in study BRF113220. Updated OS data (data cut-off March 2013) indicate that more patients benefit from combination treatment and that the benefit lasts longer compared to monotherapy treatment; due to the mechanism of preventing or delaying the onset of resistance.

The safety profile for 150/2 combination treatment is manageable with temporary dosing modifications and supportive therapy.

Based on the clinical trial data and clinical expert opinion, GSK do not believe that a <65 year age-restriction and a reference to an ECOG performance status proposed by the Delegate is warranted in the indication. Therefore we maintain that the appropriate indication for combination use is:

> *Mekinist in combination with dabrafenib is indicated for the treatment of patients with BRAFV600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma.*

A vigorous RMP together with appropriate PI for monotherapy and combination therapy adequately captures precautions and safety risks, providing dosing modification recommendations for AEs and provides measures to minimise them.

Clinical efficacy for Mekinist monotherapy has been demonstrated

The primary evidence to support the clinical efficacy of trametinib is provided by the pivotal randomised Phase III study MEK114267. In contrast to the Phase III BRAF inhibitor studies, which excluded subjects with the BRAFV600K mutation, MEK114267 was the first randomised, Phase III study to prospectively select patients with BRAFV600K-mutant melanoma. Therefore, subjects that comprise the efficacy study populations are representative of patients in Australia with unresectable or metastatic melanoma covering the two key genotypes: BRAFV600E and BRAFV600K.

In MEK114267, a statistically significant ($p<0.0001$) and clinically meaningful improvement in PFS was observed for subjects treated with trametinib compared to chemotherapy. Comparable improvements of PFS were observed for both the PE population (HR 0.44) and the ITT population (HR 0.45). A similar benefit was observed for V600E (HR 0.47) and V600K (HR 0.50) subpopulations. The difference was not statistically significant for V600K ($p=0.0788$) due to the small number of subjects per arm (trametinib: 29 points; chemotherapy: 11 points). Nonetheless, the PFS analysis suggests that trametinib has clinical utility regardless of the specific BRAF V600 mutation, and the overall PFS benefit in this study is comparable to the benefit reported for vemurafenib in the BRIM-3 study, which did not prospectively select for subjects with the BRAFV600K mutation [Chapman, 2011 [28]]. This view aligns with the FDA Division Director's Summary Review, "The magnitude of the effect on PFS observed with trametinib is similar to that with BRAF inhibitors."

In addition, GSK would like to share information from updated OS data (cut-off 20 May 2013- 64 months) which was requested by the EU Committee for Medicinal Products (CHMP) during review and shows survival is comparable for all V600 metastatic melanoma monotherapy treatments (trametinib median OS 15.6 months versus chemotherapy median OS 11.3 months, noting vemurafenib and dabrafenib median OS are 13.6 months and 18.2 months respectively [sourced from the PIs]).

The overall efficacy results suggest a clinically meaningful treatment benefit of trametinib in BRAF V600 mutation-positive melanoma patients. The Delegate's support for registration with a broad V600 indication is summarised by the following: "There is no absolute need to establish that benefit is similar for V600E and V600K. The benchmark should be whether benefit/risk in V600K is better with trametinib than that for established therapies".

Clinical safety profile is manageable for Mekinist monotherapy

Trametinib at 2 mg once daily has a manageable safety profile in the target patient population which is different to that of BRAF inhibitors. Nearly all subjects had AEs during trametinib treatment, but most AEs were manageable with supportive care, or dose reductions or interruptions; 92% of subjects received trametinib until disease progression. The overall safety profile of trametinib was similar in the pivotal and supportive studies, with regard to the types, frequency, and severity of AEs. The most common AEs in the Integrated Trametinib Safety Population included rash, diarrhoea, fatigue, peripheral oedema, nausea, and dermatitis acneiform, with most Grade 1 or 2. Of note, no related cases of cutaneous SCC have been observed, indicating that the

[28] Chapman et al. 2011. Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation. NEJM; 364:2507-16

paradoxical activation of the RAS/RAF/MAPK pathway described for small molecule BRAF inhibitors does not occur with trametinib.

AEs of special interest (AESI), which appear to be related to the MEK mode-of-action, including skin-related toxicities, diarrhoea, visual disorders, cardiac-related events, hepatic events, and pneumonitis were identified early in the development and monitoring plans as well as supportive care management guidelines were introduced in the Phase III Study MEK114267. The rate of SAEs or treatment discontinuation due to these AESIs was generally lower in MEK114267 suggesting that the monitoring and management tactics implemented for the trametinib AESI, assisted in addressing the given issues. To this end, a clinical expert, 'Expert A' states, "In clinical practice the toxicity of trametinib is manageable, with dose adjustment and monitoring by a medical oncologist."

To allow patients with melanoma to benefit optimally from trametinib prescribing physicians need to be appraised of the key risks associated with the product. Therefore, LVEF reduction/LV dysfunction, visual impairment (including retinal pigment epithelial detachment and RVO) and rash are highlighted in the Precautions section of the trametinib PI.

Other events known to be associated with trametinib, such as diarrhoea, pneumonitis, hepatic events, hypertension and oedema are listed as Adverse Reactions, and dose modification guidance is provided in the Dosage and Administration section. These events do not lead to frequent or clinically relevant dose reductions or treatment discontinuation and are amenable to risk reduction through routine patient care, patient education, and product labelling. Missing information for specific patient populations (for example, hepatic impairment, paediatric patients) are addressed in GSK's proposed RMP.

Positive benefit/risk assessment for Mekinist monotherapy

Trametinib has demonstrated a robust clinical benefit versus chemotherapy in patients with unresectable or metastatic BRAF V600 mutation-positive melanoma. The safety profile of trametinib has been well characterised and AEs related to trametinib are monitorable and manageable. BRAF treatments are the current standard of care and although in the course of clinical practice it is anticipated that the use of trametinib might be limited due to the availability of the approved BRAF inhibitors; given the clinical benefit demonstrated with trametinib and the differentiated safety profile, GSK believes strongly that the treatment option should be available for patients in the broad V600 patient population studied. For example, it is conceivable, based on a physician's and patient's judgement, that trametinib would be preferred by patients that are concerned about BRAF-induced cutaneous SCC or secondary malignancies. It should be noted that trametinib has not been studied versus the BRAF inhibitors and therefore the respective efficacy and safety profiles cannot be directly compared and caution must be exercised with cross-study comparisons due to different patient populations, sample size variations, and timing of conduct of the studies. GSK expects there will also be patients that will discontinue a BRAF-inhibitor due to toxicity (for example, pyrexia, palmar-plantar erythrodysesthesia syndrome (PPES), hyperproliferative effects and arthralgia) but could benefit from administration of trametinib monotherapy. The FDA Division Director's Summary Review states "As compared to BRAF inhibitors, trametinib has a different toxicity profile which may offer advantages to individual patients".

If the combination of dabrafenib/trametinib is approved and becomes a new treatment for subjects with BRAF mutation-positive melanoma, the use of trametinib is expected to primarily be in combination with dabrafenib. However, the safety profile of trametinib alone differs from the safety profile of the combination and therefore there will be patients who are unable to tolerate the combination due to dabrafenib-induced toxicities, and may benefit from the option of trametinib monotherapy.

In summary, trametinib is a first-in-class MEK inhibitor with a novel mechanism of action compared to BRAF inhibitors. The totality of the trametinib clinical data, generated in subjects with BRAF V600 mutant melanoma, supports an overall positive benefit/risk assessment. A second experienced medical oncologist, 'Expert B' states, "To directly address the Delegate's comment on toxicity, trametinib is efficacious with manageable toxicities".

Compelling Phase II clinical efficacy data support use of Mekinist in combination with dabrafenib

The current registration file for the combination is based on compelling efficacy data from Study BRF113220 (Phase I/II). The submission package for dabrafenib/trametinib combination treatment of melanoma (N=365) is supported by the monotherapy programs for trametinib (Safety population N=329) and dabrafenib (Safety population N=586), which were conducted in parallel in the same patient population. Two combination Phase III Studies, MEK115306 (N~340) and MEK116513 (N~694), were initiated prior to submission and are still ongoing. Expert A observes, "In my own practice I have seen patients from these Phase III trials that are far outliving the median PFS and still responding and tolerating therapy well".

The clinical results with 150/2 combination treatment indicate that more patients benefit and that the benefit lasts longer compared to monotherapy treatments; due to the mechanism of preventing or delaying the onset of resistance. Treatment with 150/2 combination resulted in a statistically significant and clinically meaningful improvement in investigator-assessed PFS compared to dabrafenib monotherapy, with an HR of 0.39 ($p<0.0001$) (median follow-up time of 14.0 months). Kaplan-Meier estimate of PFS rate at 12 months showed a larger proportion of subjects progression-free in the 150/2 combination group (41%) compared with monotherapy (9%).

In addition to the improvement in RR, in subjects who achieve a response the combination nearly doubles the response duration compared to monotherapy. In the Part C ITT population, the investigator-assessed median duration of confirmed response was 10.5 months versus. 5.6 months for 150/2 combination and dabrafenib monotherapy respectively.

The overall treatment effect (HR) of the 150/2 combination versus dabrafenib monotherapy cannot be directly compared to the treatment effect of the monotherapies, which were studied in comparison to chemotherapy. However, median PFS estimates for BRAF inhibitors used as monotherapy and dabrafenib monotherapy arm of Part C of BRF113220 have been consistent. These results provide confidence that the improvement in PFS seen with the combination compared to dabrafenib monotherapy in Part C is indicative of more effective MAPK inhibition than obtained by monotherapy.

In summary, BREAK-3 (dabrafenib) and BRIM-3 (vemurafenib) data were limited to BRAF V600E while the other MEK studies allowed subjects with the less common BRAF V600K mutation, which tends to be less responsive to MAP kinase inhibitor therapy. Evaluation of the median PFS in subjects with the V600E mutation allowed direct comparison across the studies. The median PFS in V600E subjects treated with dabrafenib monotherapy in Part C was 6.5 months, which was similar to the median PFS for subjects treated with dabrafenib on BREAK-3 (6.9 months) when an updated analysis was performed with longer duration of follow-up.

- The high ORR, higher CR rates and lack of PD as best response indicates greater effectiveness against primary resistance by the 150/2 combination treatment
- The longer PFS and extended duration of response (DoR) show a delay in occurrence of acquired resistance by the 150/2 combination treatment

- The efficacy profile for the 150/2 combination treatment surpasses the reported efficacy for monotherapy agents based on PFS, ORR and DoR
- The 150/2 combination treatment is more effective for V600K tumours than the monotherapy treatments, which have shown limited effectiveness on V600K tumours
- The 150/2 combination treatment has demonstrated limited clinical activity in BRAF-inhibitor pre-treated subjects, indicating that early combination treatment is optimal rather than sequential treatment

Updated OS analysis: The most recent OS data from BRF113220 (data cut-off 29 March 2013), suggest that the HR remains favourable for the 150/2 combination despite 83% of monotherapy patients receiving combination therapy following crossover. The more mature data provide a better understanding of the OS within the 150/2 combination group. Note, that although a median can be estimated for combination therapy, there remains considerable censoring prior to the estimated median since 52% of subjects in the 150/2 combination group remain alive. With the small sample size in both groups and allowance of crossover, the comparative results to monotherapy have not been shown to be statistically significant. Nevertheless, the trend favours the 150/2 combination arm and the estimates of OS (24 months) exceed those reported for BRAF inhibitors given as monotherapy in this population. The final analysis for OS will be conducted when 75% of deaths have been observed; projected to occur in mid-2014. With additional follow up, the estimated median OS is approximately 24 months, which exceeds published OS data for BRAF inhibitors given as monotherapy.

Safety profile for combination use is manageable

The dabrafenib (safety population N=586) and trametinib (safety population N=329) monotherapy safety databases represent a robust foundation of information in the same patient population through which the combination profile can be better understood. As such, comparisons of the randomised Phase II Part C 150/2 population of BRF113220 are made to these monotherapy safety populations. Safety data from three groups of subjects with unresectable or metastatic BRAF V600 mutation-positive melanoma are highlighted for evaluation of the safety profile for the 150/2 combination treatment (from study BRF113220).

The Part C treatment group received the full 150/2 starting dose and represent the primary safety population (N=55).

The subjects who received the full 150/2 starting dose in Parts B, C, and D were pooled to further explore the frequency and severity of AEs potentially associated with the combination (pooled 150/2 population; N=202). This population also includes Part C subjects who initially received dabrafenib monotherapy but crossed over to receive 150/2 combination (43 subjects), and includes only safety data collected during combination treatment.

The Part C dabrafenib 150 mg twice daily monotherapy treatment group (N=53) is included to allow a randomised comparison between subjects who received the combination and those who received dabrafenib monotherapy.

The key safety findings are the following: The 150/2 combination has a manageable safety profile in patients with unresectable BRAF V600 mutation-positive melanoma; although tolerability of this combination regimen is lower relative to the monotherapies requiring more frequent temporary dosing modifications to manage AEs. The types of AEs reported for this combination regimen is generally consistent with that observed with dabrafenib and trametinib as monotherapies. Pyrexia and pyrexia-related AEs are reported at a higher frequency and severity with the combination regimen but are clinically manageable with temporary dosing modifications and supportive therapy.

Hyperproliferative skin lesions including KAs and cutaneous SCC occur at a reduced frequency compared to BRAF monotherapies and with a prolonged latency in subjects receiving this combination regimen.

GSK notes that five subjects in the Integrated Summary of Safety (ISS) population aged ≥65 years and receiving treatment with 150/2 combination died from fatal SAEs; including pulmonary embolism in two subjects, intracranial haemorrhage, ventricular arrhythmia and suicide. In addition, two subjects aged ≥65 years and receiving the 150/1 dose died from fatal SAEs (sepsis, convulsion). None of these fatal SAEs were considered related to either study drug with the exception of the ventricular arrhythmia, which was considered possibly related to both study drugs. None of the events is unexpected in the older population complicated by significant medical histories. GSK has included information on elderly patients in the Clinical Trial section and the Precautions section of the PI.

Safety Update: Further safety information was provided by the safety update (data cut-off 29 March 2013). The additional safety data provide long term safety assessment of the combination for up to 29 months of combination treatment.

In summary: The profile of SAEs in the pooled 150/2 group for the safety update was similar to the ISS dataset. Pyrexia and chills were the most common SAEs in the safety update and the only SAEs that occurred in >5% of subjects. Many SAEs occurred in only one subject. There were no substantial changes in the profile of AEs leading to dose reductions or dose interruptions in the data update compared with the ISS dataset. There were no additional fatal SAEs reported in the Part C 150/2 group in the data update and no fatal SAEs have been reported for the Part D 150/2 group. The safety update data contain a substantial proportion of subjects that have been on treatment for ≥12 months. The safety update results show no clinically significant changes from the ISS dataset. At the time of the cut-off date for the Safety Update SAEs (15 August 2013), no additional subjects aged ≥65 years experienced a fatal SAE.

Positive benefit/risk assessment for combination therapy

The updated OS data suggest that the HR favours the 150/2 mg combination; with an estimated median OS around 24 months, which is impressive compared to the monotherapy median OS results. The safety of the combination has remained consistent between the updated safety data and the safety data observed in the original submission. The update provides data with a longer duration of treatment and follow up, including a substantial proportion of patients who have been treated for over one year. No new safety signals have emerged.

GSK believes the totality of the evidence presented for combination supports early approval, particularly given the high unmet medical need in the target patient population and the importance of providing early access to the combination for patients with BRAF V600 mutation-positive metastatic melanoma. Headline Phase III data will be available in the fourth quarter of 2013, with a full clinical study report (CSR) expected towards the end of the first quarter of 2014. GSK has committed to submitting this data as part of a post approval package to update the licence.

GSK feels strongly that including an age restriction on combination use is not justified. This is supported by key melanoma clinical experts who are treating patients on the aforementioned program.

Expert B states, “With respect to the restriction on treating patients >65 years of age, I strongly disagree. There is absolutely no evidence or justification to restrict these medicines to patients <65 years of age. The data shows that just one patient >65 years suffered a drug-related fatal SAE while on combination therapy and this 69 year old male had a substantial history of cardiac problems and was assessed by the investigator as only “possibly related”. Moreover I do not believe the cardiac safety data on the

dabrafenib/trametinib combination indicate any restriction in use based on age. From clinical experience, this combination is manageable and would benefit patients >65 years of age who are otherwise not contraindicated."

Expert A adds, "It would not be appropriate, to discriminate on an arbitrary age cut-off for example 65, and I think this would be very difficult situation to counsel a "well" patient over 65 that they could not have the best available therapy based on their age. While there is a slightly higher AE risk over the age of 65, this is well known in all of the literature that older patients have more AEs from all anti-cancer therapies, it does not mean they do not obtain clinical benefit."

In summary, the 150/2 mg combination provides an important treatment with a favourable benefit/risk for patients with advanced or metastatic BRAF V600 mutation-positive melanoma. Expert B summarises with, "As a clinician, I am confident that the combination is safe, and that pyrexia is clinically manageable with treatment breaks, use of non-steroidal anti-inflammatory drugs and in some cases low dose corticosteroids. From my clinical perspective, the benefits far outweigh the risks."

Indication and conclusion

GSK concurs with the Delegate that the favourable benefit/risk assessment demonstrated in these studies supports registration of Mekinist as a monotherapy and in combination with dabrafenib for patients with V600 mutation-positive unresectable or metastatic melanoma; the latter represents a significant improvement over available monotherapies.

Based on the totality of the data for trametinib monotherapy, and the advice from melanoma clinical experts, GSK's preference is for an indication to be broad enough to allow the physician to make the treatment decision based on clinical need. Expert A states, "In clinical practice there is a role for trametinib monotherapy as first line therapy. In this difficult to treat disease, it is important for a physician to have numerous treatment options available for first line therapy. This provides the physician with flexibility to derive a specific treatment plan for individual patients based on their medical history and consideration of the different toxicity profiles of treatment options".

Expert B concurs, "it is advantageous to have a broader indication for trametinib monotherapy, which allows the physician to treat based on patients individual needs".

For combination use, GSK has aforementioned and included a justification as to why we believe an age restriction is not clinically ethical and reference to an ECOG performance status may be clinically challenging. Expert B says, "I would caution against including an ECOG performance status cut-off which is too low as this can be a difficult clinical assessment. For your information, I would certainly feel comfortable treating patients with combination therapy who were ECOG 2."

Expert A also advises, From an age perspective, there are some patients into their 80's who have a performance status of 0, adequate renal, liver and cardiac function for whom combination therapy is appropriate, just as there are some 50 year olds who because of co-morbities, would not be suited to combination or any therapy".

Therefore, for registration, we would like to propose the following indication:

> *Mekinist as a monotherapy is indicated for the treatment of patients with BRAFV600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma.*
>
> *Mekinist as monotherapy has not demonstrated clinical activity in patients who have progressed on BRAF inhibitor therapy (see Clinical Trials).*
>
> *Mekinist in combination with dabrafenib is indicated for the treatment of patients with BRAFV600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma.*

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Mekinist film coated tablets containing 0.5 mg, 1 mg and 2 mg of Trametinib (as DMSO) to have an overall positive benefit/risk profile for the amended indication**;**

> *Mekinist as a monotherapy is indicated for the treatment of patients with BRAFV600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma who are intolerant of BRAF inhibitors or for whom BRAF inhibitors are contraindicated.*
>
> *Mekinist as monotherapy has not demonstrated clinical activity in patients who have progressed on BRAF inhibitor therapy (see Clinical Trials).*

In making this recommendation the ACPM;

- Noted the exclusion of patients with brain metastases in trials was considered problematic as a significant percentage of those in the clinical population will have such involvement and there is little experience from the trials for the reassurance of prescribers.

The ACPM taking into account the submitted evidence of efficacy, safety and quality considered Mekinist to have an uncertain benefit/risk profile at this time for the indication;

> *Mekinist in combination with dabrafenib is indicated for the treatment of patients less than 65 years of age, with ECOG performance status 0-1 and with BRAFV600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma.*

In making this recommendation the ACPM:

- Noted that while the pivotal trial was randomised against active comparators, it was only a small Phase II study and provided immature data with limited OS efficacy data as well as minimal safety data.
- Noted that the limited data available from the trial population may mean that toxicity increases in the wider clinical population to be treated.
- Expressed considerable concern over the level of toxicity reported. This is a small dataset on which to base regulatory safety for a combination of two novel chemical entities.

The ACPM advised that registration of the combination regimen ideally should wait on further data, in particular safety data.

The committee was requested to provide advice on the following specific issues:

1. For trametinib, efficacy appears comparable to that seen with BRAF inhibitors (perhaps better for V600K disease), but toxicity appears worse. In what advanced melanoma population (if any) does trametinib monotherapy have a positive benefit/risk balance?

   While the data from the small, Phase I and II trials submitted suggest efficacy similar to, and in the case of V600K mutation tumours perhaps better than, other BRAF inhibitors these data are very limited. The toxicity reported thus far is high. Given the uncertain benefit/risk balance due to high levels of toxicity, the ACPM advised this treatment is suitable only in high risk patients.

2. For combination therapy, evidence is based on a limited number of trials, with limited sample size and follow-up. Phase III studies are progressing. Are efficacy and safety data reliable based on the submitted data?

   The ACPM were of the view that Phase III trials would better define the benefit/risk profile and provide more reassurance of benefit.

3. If the committee considers efficacy and safety data reliable for combination therapy, in what population of advanced melanoma patients (if any) is there a positive benefit/risk balance for combination therapy?

   The ACPM remains unconvinced of benefit compared to toxicity.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Post ACPM discussion

GSK response to ACPM resolutions

After this advice was received, the TGA requested further data from GSK to support use of the dabrafenib/trametinib combination which includes minutes of a post-ACPM advice teleconference with the sponsor. The new data offered by the sponsor were from the Combi-D Study.

The sponsor has responded to the concerns of ACPM, in a consolidated post-ACPM response. This response was a summary of ACPM concerns and cross-reference to the Combi-D top-line results.

Top-line results from Combi-D

The sponsor has provided top-line results from a Phase III study of trametinib used in combination with dabrafenib. Combi-D results are set out below. The formal CSR has not been evaluated; only the sponsor's 'top-line results' have been reviewed.

Study design

- Randomised, double-blind study. Randomisation was stratified by LDH level (high or normal) and tumour BRAF mutation (V600E versus V600K).

Inclusions/exclusions

- Patient with histologically confirmed cutaneous melanoma, either Stage IIIC (unresectable) or Stage IV.
- Patients who had received prior systemic treatment in the advanced or metastatic setting were not eligible.

Interventions

Patients were randomised 1:1 to either:

- Dabrafenib (150 mg twice daily) + trametinib (2 mg once daily) "combination", or
- Dabrafenib "monotherapy" (150 mg twice daily)

Dabrafenib was in the HPMC capsule (that is the marketed version).

Cross-over was not allowed.

Methods

The primary endpoint was PFS by investigator assessment. A BIRC allowed sensitivity analysis of PFS.

ORR, DoR, OS, safety and PK were secondary study objectives.

The study was over-enrolled by 24% and the sponsor amended the analysis plan "to improve the precision of the median PFS estimate in combination therapy arm".

The analysis at the time of final PFS analysis is 'interim' in that final OS analysis has not been conducted. The data-cut off for information below is 26 August 2013.

Patient characteristics

There were 211 subjects in the ITT population for the combination arm and 212 in the monotherapy arm. In the V600E mutation-positive analysis set, there were 179 and 181 patients respectively. In the V600K mutation-positive analysis set, there were 32 and 30 patients respectively.

Mean age was 55 years in both arms; 71-73% of subjects were 18-64 years of age; 20-21% were 65-74 years; and 5-8% were 75-84 years. 46-47% of subjects were female. Baseline disease characteristics are summarised below:

Table 23: Baseline disease characteristics

	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)

Study results – efficacy

As of the data cut-off, 19% of combination subjects and 26% of monotherapy subjects had died. Subject disposition is summarised below:

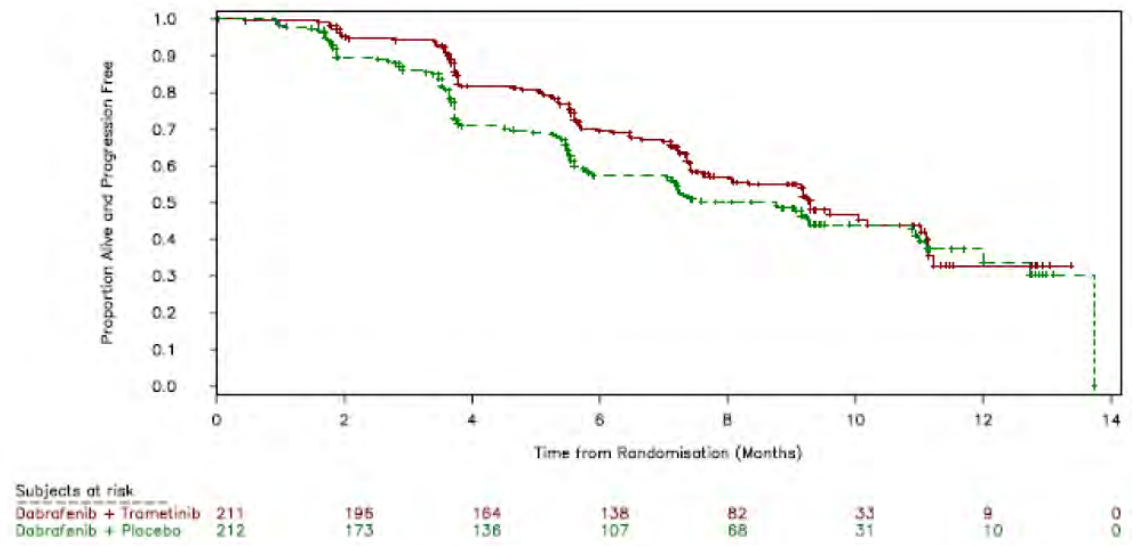
Table 24: Subject disposition

	Dabrafenib + Trametinib (N=211)	Dabrafenib + Placebo (N=212)
Subject status		
Died	40 (19)	55 (26)
Ongoing	154 (73)	147 (69)
On study treatment	111 (53)	90 (42)
In follow-up	43 (20)	57 (27)
Withdrawn from study	17 (8)	10 (5)
Primary reason for withdrawal		
Study closed/terminated	0	0
Lost to follow-up	4 (2)	3 (1)
Investigator discretion	2 (<1)	2 (<1)
Withdrew consent	11 (5)	5 (2)

Progression-free survival

Median PFS was 9.3 months for the combination arm, versus 8.8 months for the monotherapy arm. The HR was 0.75 (95% CI 0.57-0.99). The KM curve follows:

Figure 25: Kaplan-Meier curve – of progression-free survival



Sensitivity analysis using BIRC outcomes was as follows: median PFS 10.1 months for the combination arm, 9.5 months for the monotherapy arm (HR 0.78. 95% CI 0.59-1.04).

Other sensitivity analyses produced median PFS in the range 9.2-9.3 months for combination, 7.2-7.6 months for monotherapy. Despite the lower values for the monotherapy arm (relative to primary analysis), HRs in these sensitivity analyses remained around 0.71-0.73, that is, fairly consistent with the primary analysis.

Overall response rate

This is summarised below, and favours combination therapy:

Table 26: Overall response rate

	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	

Overall survival

The HR for death was 0.63 (95% CI, 0.42-0.94). This was from an interim analysis, at which time 19% (combination) versus 26% (monotherapy) of study subjects had died. Median follow-up time was approximately nine months in each arm; median OS had not been reached in either arm.

Study results – safety

Exposure

Median time on study treatment was eight months for combination and seven months for monotherapy, with more detail provided as follows:

Table 27: Median time on study treatment

	Combination Therapy	Monotherapy
< 3 months	16 (8)	34 (16)
3-6 months	44 (21)	57 (27)
> 6-12 months	133 (64)	110 (52)
> 12 months	16 (8)	10 (5)

Exposure to dabrafenib was similar across arms (median 298 mg daily dose for the combination arm, 300 mg for the monotherapy arm).

Overview

The following table overviews AEs across arms:

Table 28: Overview of adverse events across arms

	Dabrafenib + Trametinib (N=209)	Dabrafenib + Placebo (N=211)
Any AE	199 (95)	203 (96)
AEs related to study treatment	179 (86)	186 (88)
AEs leading to permanent discontinuation of study treatment	19 (9)	11 (5)
AE leading to dose reduction	51 (24)	28 (13)
AE leading to dose interruption	94 (45)	63 (30)
Any SAE	73 (35)	64 (30)
SAEs related to study treatment	54 (26)	48 (23)
Fatal SAEs	4 (2)	0
Fatal SAEs related to study treatment	0	0

As noted by the sponsor, dose interruption (45% in Combi-D, for combination use) was resorted to less often than in BRF113220 Part C; likewise there was less call for dose reduction (24% versus 49% respectively).

Common AEs

These are summarised below.

Table 29: Common adverse events

Preferred term	Dabrafenib + trametinib (n=209)	Dabrafenib + placebo (n=211)
Any event	199 (95)	203 (96)
Pyrexia	107 (51)	59 (28)
Fatigue	74 (35)	74 (35)
Headache	63 (30)	62 (29)
Nausea	63 (30)	54 (26)
Chills	62 (30)	33 (16)
Arthralgia	51 (24)	58 (27)
Diarrhoea	51 (24)	30 (14)
Rash	48 (23)	46 (22)
Hypertension	46 (22)	29 (14)
Vomiting	42 (20)	29 (14)
Cough	34 (16)	35 (17)
Pain in extremity	30 (14)	33 (16)
Oedema peripheral	30 (14)	10 (5)
Decreased appetite	23 (11)	25 (12)
Myalgia	22 (11)	24 (11)
Constipation	22 (11)	18 (9)
Abdominal pain	22 (11)	14 (7)
Alanine aminotransferase increased	22 (11)	10 (5)
Aspartate aminotransferase increased	22 (11)	7 (3)
Asthenia	20 (10)	27 (13)
Nasopharyngitis	20 (10)	15 (7)
Dizziness	20 (10)	12 (6)

There is a notable difference in the incidence of pyrexia (51% in the combination arm, including 6% Grade 3; versus 28% in the monotherapy arm, with 2% as Grade 3). For chills there was a similar pattern. There was also more diarrhoea, vomiting, hypertension, peripheral oedema and liver function test (LFT) derangement in the combination arm. These imbalances were offset by a lower rate in the combination arm of alopecia, hand-foot syndrome and skin papilloma.

Pyrexia commonly led to dose reduction or interruption, in the combination arm. In 5/209 (combination) versus 2/211 (monotherapy), pyrexia lead to permanent drug discontinuation.

AEs in the elderly

In the combination arm, patients 65+ years of age had disproportionately more AEs, SAEs, severe/life-threatening AEs and AEs leading to permanent discontinuation, than those patients <65 years of age.

Peripheral oedema was more common in patients 65+ years (23%, combination arm) than in patients <65 years (11%, combination arm).

Grade 3-4 AEs were distinctly more common (in the combination arm) in older patients (25% in subjects <65 years; 53% in subjects 65+ years). Hypertension was an AE that contributed to this differential (<1% versus 13%, respectively).

Ocular AEs leading to permanent discontinuation were more prominent in older subjects, in the combination arm (individual AEs included chorioretinal disorder, iridocyclitis, retinopathy and blurred vision); similarly, LFT derangements leading to treatment discontinuation were relatively more common in older subjects.

AEs of interest

Table 30: Adverse events of special interest as defined by the sponsor

	Dabrafenib + Trametinib			Dabrafenib + Placebo		
Category (any event)	**Grade 3**	**Grade 4**	**Total**	**Grade 3**	**Grade 4**	**Total**
Skin Related Toxicities	0	0	84 (40)	4 (2)	0	98 (46)
Hepatic Disorders	10 (5)	0	28 (13)	2 (<1)	0	15 (7)
Diarrhea	2 (<1)	0	51 (24)	2 (<1)	0	30 (14)
Ocular Events	2 (<1)	0	22 (11)	0	0	23 (11)
Cardiac Events	1 (<1)	0	9 (4)	1 (<1)	0	7 (3)
Pneumonitis	0	0	1 (<1)	0	0	0
Hypertension	8 (4)	0	46 (22)	10 (5)	0	29 (14)
Oedema	2 (<1)	0	37 (18)	1 (<1)	0	12 (6)
Haemorrhages	2 (<1)	1 (<1)	35 (17)	3 (1)	0	27 (13)
Hypersensitivity	0	0	12 (6)	0	0	6 (3)
Pyrexia	13 (6)	0	116 (56)	4 (2)	0	65 (31)
CuSCC	4 (2)	0	5 (2)	7 (3)	1 (<1)	20 (9)
Non-Cutaneous Treatment Emergent Malignancies	1 (<1)	0	2 (<1)	2 (<1)	0	3 (1)
New Primary Malignant Melanoma (Cutaneous)	1 (<1)	0	1 (<1)	0	0	3 (1)
Basal Cell Carcinoma	3 (1)	0	4 (2)	5 (2)	0	8 (4)
Renal Failure	2 (<1)	0	7 (3)	0	0	4 (2)
Uveitis	0	0	2 (<1%)	0	0	3 (1%)
Pancreatitis	0	0	1 (<1)	1 (<1)	0	1 (<1)
Hyperglycaemia	4 (2)	0	13 (6)	1 (<1)	0	2 (<1)
Neutropenia	8 (4)	1 (<1)	22 (11)	1 (<1)	1 (<1)	4 (2)
Pulmonary Embolism	1 (<1)	1 (<1)	2 (<1)	1 (<1)	0	1 (<1)
Rash	0	0	72 (34%)	0	0	64 (30%)

There were four fatal AEs; these were all in the combination arm, though none were ascribed to treatment. The fatal AEs were: stroke on Study Day 125 (International normalised ratio (INR) 2.5 on warfarin on admission; brain metastases present); pneumonia on Study Day 21 (baseline mild pulmonary fibrosis); stroke on Study Day 123 (brain metastases present); and stroke on Study Day 143 (brain metastasis status unreported).

It is also of note that 'ejection fraction decreased' was seen in 6/209 (3%) in the combination arm and 5/211 (2%) in the monotherapy arm. Hypotension and syncope were both seen more often in the combination arm than in monotherapy, as SAEs.

Comments about Combi-D top-line results

A prominent outcome of Combi-D was a higher than expected median PFS in the dabrafenib monotherapy arm.

In BRF113220 Part C, as assessed by the investigator, median PFS was 9.4 months in the 150/2 arm, 9.2 months in the 150/1 arm and 5.8 months for dabrafenib monotherapy. In Combi-D, the median PFS was 9.3 months (150/2) versus 8.8 months (monotherapy). Given the similar patient populations under study, this is quite a distinct difference. BREAK-3 (a Phase III trial supporting dabrafenib monotherapy) reported median PFS of 6.9 months (for V600E).

Despite this outcome in Combi-D, there was a statistically significant improvement in PFS with combination therapy over dabrafenib monotherapy (the upper limit of the 95% CI

around the PFS HR was 0.99). It could be argued that the difference in median PFS was not clinically significant; but the HR estimate of 0.75 was in the Delegate's opinion clinically significantly less than 1, so overall the Delegate considered Combi-D to have shown a clinically relevant improvement in PFS with dabrafenib/trametinib, over dabrafenib alone.

ORR results support the view that combination therapy provides a relevant degree of added efficacy. Although there was no real difference in the rates of CR across arms, there were more PRs in the combination arm than with monotherapy. (DoR was not noted in Combi-D top-line results.)

OS results were, as with BRF113220, immature, but early data are consistent with an OS benefit and, importantly, are consistent with the magnitude of effect reported in BRF113220 Part C. Interestingly, the OS effect seen in the early study was despite 80% cross-over to combination, but in Combi-D cross-over was not allowed within the trial.

Other studies

The sponsor is conducting another Phase III, randomised study of combination therapy in advanced BRAF V600 mutation-positive melanoma, namely COMBI-v (MEK116513), where dabrafenib/trametinib are being compared with vemurafenib. The primary endpoint is OS. Interim analysis is forecast to be conducted within the second quarter of 2014.

Limitation of use: Mekinist as a single agent is not indicated for treatment of patients who have received prior BRAF-inhibitor therapy.

Conclusions – combination therapy

The ACPM's concerns regarding combination therapy were:

- Limited sample size in BRF113220 Part C
- Median follow-up in that study of only 14 months (although the most recently available OS analysis included 24 month median follow-up), that is, immature data
- Minimal safety data, which pointed to significant toxicity

The Delegate accepted these concerns and chose to await further data supporting use of the combination therapy.

Only top-line results for Combi-D are available, but the Delegate now considers the results overcome the objections raised by ACPM, as follows:

- A substantial number of patients have been randomised to combination therapy in Combi-D (n=211, versus n=54 subjects who received the proposed combination dose in BRF113220 Part C).
- Median follow-up in Combi-D was nine months, shorter than in BRF113220 Part C. Thus, while the total number of exposed patients has increased, there is still limited experience with 'long-term' use of combination therapy. This is in the context of treatment of advanced melanoma, which historically has a grave prognosis. It can still be argued that efficacy data for combination use (that is dabrafenib/trametinib) are 'immature' however two studies have now provided the suggestion of an OS benefit, namely: BRF113220 Part C (HR 0.67 favouring the combination) and Combi-D (HR 0.63).
- Significant additional safety data are available even in the 'top-line' Combi-D results, and these reveal no outstanding additional concerns.

The Delegate was satisfied that the benefit/risk balance is positive for combination therapy in the patient group defined by the following indication:

> *Mekinist in combination with dabrafenib is indicated for the treatment of patients with BRAFV600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma.*

The Delegate accepts that the increased toxicity in older patients and those with lower overall performance status can be managed via Precautions in the PI.

Areas of uncertainty include:

- Explanation for the variable median PFS with dabrafenib across multiple studies;
- Efficacy by V600E versus V600K status in Combi-D;
- Efficacy and safety by performance status in Combi-D; and
- Whether there exist updated data (for example, OS) from BRF113220 Part C.

Conclusions – monotherapy

The sponsor modifies the proposed monotherapy indication as follows:

> *Mekinist as monotherapy is indicated for the treatment of patients with BRAFV600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma.*
>
> *Mekinist has not been compared with a BRAF inhibitor in a clinical study in patients with unresectable or metastatic melanoma. Mekinist has been associated with the certain serious adverse effects not observed with BRAF inhibitors (see Precautions and Adverse Effects).*
>
> *Mekinist as monotherapy has not demonstrated clinical activity in patients who have progressed on BRAF inhibitor therapy (see Clinical Trials).*

In other words, GSK does not favour restriction of monotherapy use to those patients who are intolerant of BRAF inhibitors or for whom BRAF inhibitors are contraindicated.

While in the pre-ACPM response the sponsor's position is that overall PFS benefit for trametinib monotherapy is similar to that of BRAF inhibition, it should be noted that dabrafenib monotherapy is now linked to a range of median PFS outcomes, from 5.8 months (BRF113220 Part C) to 6.9 months (BREAK-3) to 8.8 months (in Combi-D) in broadly similar patient populations. The pivotal MEK114267 study's trametinib monotherapy arm had a median PFS of 4.8 months.

Further, despite the limitations of cross-study comparison, there is a suggestion of better survival benefit with BRAF inhibition than with trametinib monotherapy (median OS 15.6 months for trametinib in MEK114267, cut-off 20 May 2013; 18.2 months for dabrafenib monotherapy in BREAK-3).

Toxicity profiles of trametinib and dabrafenib monotherapy vary, but the Delegate considers toxicity of trametinib to be greater. For example, the rate of discontinuation due to AEs is higher with trametinib.

The Delegate is not satisfied that the benefit/risk balance of trametinib monotherapy supports use as proposed by the sponsor. Individual patients may have specific reasons why BRAF inhibition is not appropriate, but the Delegate considers the following indication covers those situations:

> *Mekinist as a monotherapy is indicated for the treatment of patients with BRAFV600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma and in whom either there is intolerance to BRAF inhibitors or BRAF inhibitors cannot be used.*
>
> *Mekinist as monotherapy has not demonstrated clinical activity in patients who have progressed on BRAF inhibitor therapy (see Clinical Trials).*

The indication above does not consign trametinib as monotherapy to use only in patients where BRAF treatment has been given.

Trametinib monotherapy has no role where BRAF inhibitors have been used but have proven inefficacious (that is, where there has been progression).

Trametinib monotherapy could be given where BRAF inhibitors are formally contraindicated (where there is a hypersensitivity issue), but more broadly where BRAF inhibitors cannot be used (this gives considerable scope to the clinician to make individualised judgements about whether BRAF inhibition is suitable, that is, can be used).

Trametinib monotherapy could be given where BRAF inhibition has been tried but has met with intolerance, such as, unacceptable/unmanageable toxicity.

RMP

The sponsor notes ACPM's concern:

> The RMP evaluator suggested that the sponsor's RMP was generally acceptable but recommended greater vigilance concerning use in patients with heart failure and better communication of clinical monitoring requirements (skin/cardiac/ocular/pulmonary) in the PI. The ACPM endorsed these recommendations fully.

The sponsor states in response:

> Please cross refer to the EU RMP for consideration. Please note that this document is still considered draft since it represents the EU RMP at the D180 stage of the ongoing EU procedure; with this version to be submitted as part of the D180 response package. Please also note that the EU Summary of Product Characteristics (SmPC) has not been included in Annex 2 since the document is not yet complete. When completed the updated SmPC can be forwarded for information.
>
> The RMP has been updated with respect to comments from CHMP and ACPM. The PI will also address the appropriate safety concerns.

The sponsor stated in an email dated 20 January 2014 that the latest draft of the EU-RMP was available.

In the approval letter the Delegate referred to the version that has already been accepted by the RMP Evaluation Section. The Delegate asked that updates to the RMP be submitted to the TGA for evaluation.

Product Information

The PI should clearly communicate the higher risk of AEs in older patients and those with lower performance scores.

Related submissions

Regarding the Combi-D study, the sponsor also notes:

> A 'post-approval' submission is proposed to submit the full CSR to update the PI.

There should also be an application to extend the indications of dabrafenib to reflect combination use.

There should be a commitment to submit data from Combi-v, when available.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Mekinist containing trametinib dimethyl sulfoxide 0.5 mg, 1 mg and 2 mg, indicated for:

> *Mekinist in combination with dabrafenib is indicated for the treatment of patients with BRAFV600 mutation positive unresectable Stage 111 or metastatic (Stage IV) melanoma.*
>
> *Mekinist as a monotherapy is indicated for the treatment of patients with BRAFV600 mutation positive unresectable Stage III or metastatic (Stage IV melanoma and in whom either there is intolerance to BRAF inhibitors or BRAF inhibitors cannot be used.*
>
> *Mekinist as monotherapy has not demonstrated clinical activity, in patients who have progressed on BRAF inhibitor therapy (see Clinical Trials).*

Specific conditions applying to these therapeutic goods

The Mekinist® EU Risk Management Plan (EU-RMP), version 0.0 (dated 31/01/2013, DLP 25/09/2012), included with submission PM-2012-04134-1-4, with Australian Specific Index (ASA) Version 1 and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1: Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2: Extract from the Clinical Evaluation Report

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