Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Dabrafenib mesilate

Proprietary Product Name: Tafinlar

Sponsor: GlaxoSmithKline Australia Pty Ltd

Date of CER: 20 February 2013

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 the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
a.k.a.	Also known as
AE	Adverse event
AML	Acute myeloid leukaemia
AMS	Accelerator mass spectrometry
ARF	Acute renal failure
ATP	Adenosine triphosphate
AUC	Area under the plasma drug concentration-time curve
AUC(0-∞)	Area under the concentration-time curve from zero to infinity
AUC(0-τ)	Inter-dose interval area under the concentration-time curve
BCC	Basal cell carcinoma
Bcrp	Breast cancer resistance protein
BCS	Biopharmaceutics Classification System

Abbreviation	Meaning
BID	Twice a day
BRAF	A member of the RAF kinases
Cavg	Average concentration
CL/F	Apparent oral clearance (L/h)
CL_0	Initial (non-inducible) clearance (L/h)
CL_{ind}	Inducible clearance (L/h)
Cmax	Maximum observed concentration
CPH	Cox proportional hazards
CR	Complete response
CSR	Clinical Study Report
Cτ	Pre-dose (trough) concentration at the end of the dosing interval
CT	Computed tomography
Ctrough	Trough concentration
CYP	Cytochrome P450
DTIC	dacarbazine
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
ED50	Daily dose resulting in 50% of maximum response
EMA	European Medicines Agency
Emax	Maximum response
ERK	Extracellular signal regulated kinase
EU	European Union
F	Absolute bioavailability
FDG-PET	Fluorodeoxyglucose-positron emission tomography

Abbreviation	Meaning
FTIH	First time in humans
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
HPMC	hydroxypropylmethylcellulose
HR	Hazard ratio
HRQoL	Health-related quality of life
IIV	Inter-individual variability
IR	Independent review
ISS	Integrated summary of safety
ITT	Intention-to-treat
IUO	Investigational use only
IV	Intravenous
Ka	Absorption rate constant (L/h)
LDH	Lactate dehydrogenase
LLE	Liquid-liquid extraction
LLQ	Lower limit of quantification
LS	Least squares
LVEF	Left ventricular ejection fraction
MAPK pathway	The RAS/RAF/MEK/ERK pathway (MAP kinase pathway)
MEK	Mitogen-activated ERK kinase
MRI	Magnetic resonance imaging
OIRR	Overall intracranial response rate
ORR	Overall response rate
OS	Overall survival
pERK	Phosphorylated ERK

Abbreviation	Meaning
PD	Progressive disease
PFS	Progression-free survival
Pgp	p-glycoprotein
PK	Pharmacokinetics
PPE	Palmar-plantar erythrodysaethesia
PPT	Protein precipitation
PR	Partial response
QTc	Corrected QT interval on electrocardiogram
RAF	A MAP kinase kinase kinase (MAP3K) that functions downstream of RAS to activate MEK. Has isoforms including A-, B- and C-RAF or RAF-1
RAS	A GTPase which activates RAF kinases
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SD	Stable disease
SRS	Stereotactic radiosurgery
SUVmax	Maximum standard uptake value
t½	Terminal phase half-life
τ	Dosing interval
TGA	Therapeutic Goods Administration
TID	Three times daily
Tlag	Absorption lag-time (h)
tmax	Time of occurrence of Cmax
TS	Tumour size
UHPLC/MS/MS	Ultra high-performance liquid chromatography with tandem mass spectroscopic detection

Abbreviation	Meaning
ULN	Upper limit of normal
USA	United States of America
Vc/F	Apparent volume of distribution of central compartment (L)
Vdss	Volume of distribution at steady state
Vp/F	Apparent volume of distribution of peripheral compartment
WBRT	Whole brain radiotherapy
WT	Wild type

1. Introduction

This is a submission to register the new active substance dabrafenib mesilate.

Dabrafenib (code GSK2118436) is a potent, selective, ATP-competitive inhibitor of mutant RAF kinases including $BRAF^{V600E}$, $BRAF^{V600K}$ and $BRAF^{V600D}$ mutations. Oncogenic mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway (a.k.a MAP kinase pathway) and stimulation of tumour growth.

The proposed indication is for the treatment of patients with BRAF V600 mutation positive unresectable or metastatic (Stage IV) melanoma.

The recommended dose is 150mg twice daily by oral administration (corresponding to a total daily dose of 300mg). The dose should be taken either at least one hour before, or at least two hours after a meal, with approximately 12 hours between doses. Treatment should continue until disease progression or the development of unacceptable toxicity.

Dabrafenib has been designated as an orphan drug (on 30 May 2012), with the indication *for the treatment of patients with BRAF V600 mutation positive unresectable or metastatic (Stage IV) melanoma.*

The indication for dabrafenib sought in this submission is synonymous with the designated orphan indication.

2. Clinical rationale

Advanced melanoma (unresectable Stage III or metastatic Stage IV) has a poor prognosis, with a 2008 meta-analysis of comparator arms in Phase II metastatic melanoma trials[1] finding a median progression-free survival (PFS) of 1.7 months, and a median overall survival (OS) time of 6.2 months. BRAF mutations have been found to occur in approximately 50% of melanomas[2].

[1] Korn EL, Liu P-Y, Lee SJ, Chapman J-AW, Niedzwiecki D, Suman VJ et al. Meta-analysis of Phase II cooperative group trials in metastatic Stage IV melanoma to determine progression-free and overall survival benchmarks for future Phase II trials. *Journal of Clinical Oncology,* 2008;26:527-34.
[2] Ascierto P, Kirkwood J, Grob J, et al. The role of BRAF V600 mutation in melanoma. *Journal of translational medicine*, 2012; 10:85

The clinical rationale for dabrafenib as stated by the Sponsor in the application letter is that unresectable or metastatic melanoma is refractory to most currently available anticancer agents, with a poor response to currently available systemic agents including chemotherapy and immunotherapy, and radiation and hormonal therapy having a limited, palliative role. The Sponsor claims that although the treatment of advanced melanoma will improve with the availability of ipilimumab and vemurafenib, there is still high unmet medical need for alternative approaches to the treatment of advanced melanoma.

Comment: It is acknowledged prior to the registration in Australia of ipilimumab in July 2011 and vemurafenib in May 2012, there were limited effective treatments available for advanced melanoma. However these recent additions have provided alternative more efficacious treatments. It is noted that the current submission compares dabrafenib with the older treatments which were standard care at the time of drug development. However, an assessment also needs to be made of the benefit of dabrafenib with respect to these newer treatments.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical dossier documented a full clinical development program for pharmacology, efficacy and safety studies.

The submission contained the following clinical information:

Module 5:

- 6 clinical pharmacology studies (2 of which are interim reports), including 6 that provided pharmacokinetic data and 1 that provided pharmacodynamic data.
- 1 population pharmacokinetic analysis, and 1 covariate PK analysis of dabrafenib metabolites.
- 1 exposure response analysis (PK/PD) study.
- 1 pivotal efficacy/safety study: BRF113683 (BREAK-3).
- 1 dose-finding study: BRF112680.
- 2 supportive efficacy/safety studies: BRF113710 (BREAK-2) and BRF113929 (BREAK-MB)
- 3 other studies with safety results: BRF113220 (combination with trametinib), BRF113928 (Phase II BRAF positive non-small cell lung cancer), and BRF114144 (rollover).

Module 1

- Application letter, application form, draft Australian PI and CMI, draft FDA product label, draft European Summary of Product Characteristics

Module 2

- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

Comment: It is noted that the pivotal study (BRF113683, BREAK-3) and the two supportive studies (BRF113710, BREAK-2 and BRF113929, BREAK-MB) contained an exploratory analyses of BRAF mutation in circulating cell-free DNA. This information was not evaluated in this CER, as it was not considered by the evaluator to be relevant to the current application.

3.2. Formulation

As reported by the Sponsor in the Clinical overview:

'In all clinical studies, dabrafenib was administered as the mesylate salt of dabrafenib and using micronised drug substance. Initially, dabrafenib formulation was encapsulated using gelatin shell. The capsule shell was later changed to hypromellose (hydroxypropylmethylcellulose or HPMC) due to a decrease in dissolution observed over time with gelatin capsules. HPMC capsules were used in BREAK-MB, the Phase II study in subjects with BRAF mutation-positive metastastic melanoma to the brain, and in BREAK-3, the Phase III study. Capsules administered in BREAK-2, the Phase II study in subjects with BRAF mutation-positive metastatic melanoma, were gelatin capsules. The intended commercial formulations are 50 mg and 75 mg immediate release HPMC dabrafenib capsules to support the recommended oral dose of 150 mg BID and any dose modifications. The only difference between clinical formulations used in BREAK-3 and BREAK-MB and the proposed commercial formulations is that the commercial capsules will be printed with an identifying code.'

'The bioavailability of dabrafenib was 2.02- and 1.80-fold higher maximum observed plasma concentration (Cmax) and area under the plasma drug concentration-time curve (AUC) measured to infinity (0-∞), respectively, after single dose administration as HPMC capsules compared to gelatine capsules.'

Comment: The formulation proposed for marketing in Australia is identical to that used in the pivotal Phase III study (BREAK-3). The effect of the gelatine formulation used in the earlier clinical trials was a lower bioavailability of dabrafenib compared to formulation as HPMC capsules, and this is discussed in Section 4.2.2.2.3.

3.3. Guidance

A pre-submission meeting between TGA/Medsafe and GSK to discuss dabrafenib [**information redacted**] occurred on 12th April 2012. During this meeting, the pivotal and supporting studies for the use of dabrafenib were described, with regards to their design and suitability as supporting data for the proposed submission. No outstanding issues were identified from the meeting minutes.

In this meeting, it was agreed that the proposed indication would be for a broad V600 mutation positive population, and that the use of progression-free survival (PFS) as the primary endpoint was acceptable and in line with the TGA-adopted EU Guideline on the evaluation of human anticancer medicines in man.

3.4. Paediatric data

The submission did not include paediatric data. However, details for a Paediatric Development Program for the treatment of adolescents with BRAF V600 mutant melanoma and paediatric patients with solid malignant BRAF V600 mutation-positive tumours were provided.

3.5. Good clinical practice

The Sponsor declared that all studies referred to in this application complied with the principles of Good Clinical Practice, and conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was reported to have occurred for all subjects, and the studies performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted.

No evidence was found by this evaluator to contradict this claim.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic.

Table 1. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	-	-
PK in subjects with solid tumours	General PK - Single dose	BRF112680 BRF113479 ‡ BRF113463 BRF113771 ‡
	- Multi-dose	BRF112680 BRF113771 ‡
	Bioequivalence† - Single dose	BRF113468 (particle size, capsule type) ‡
	- Multi-dose	-
	Food effect	BRF112680 BRF113468 ‡
PK in special populations	Target population § - Single dose	BRF113479 BRF113463 BRF113771
	Multi-dose	BRF112680
	Hepatic impairment	-
	Renal impairment	-
	Neonates/infants/children/ adolescents	-
	Elderly	Population PK analysis
Genetic/gender-related PK	Males vs. females	Population PK analysis
PK interactions	Midazolam	BRF112680

PK topic	Subtopic	Study ID
	Ketoconazole	BRF113771
Population PK analyses	Healthy subjects	-
	Target population§	Population PK analysis Covariate metabolite analysis

† Bioequivalence of different formulations.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.
‡ Dabrafenib formulated as HPMC capsules

Table 2 lists pharmacokinetic results that were excluded from consideration due to study deficiencies.

Table 2. Pharmacokinetic results excluded from consideration.

Study ID	Subtopic(s)	PK results excluded
BRF113220	PK of dabrafenib in combination with trametinib	Data not relevant to the indication proposed in this submission; more details needed

Pharmacokinetic data was also obtained from the pivotal efficacy Phase III study (BRF113683), and the supportive Phase II efficacy studies (BRF113710 and BRF113929,). These studies were not designed as PK studies, but sparse sampling methods were used to collect PK data on a subset of subjects which was analysed. See the review of the Population PK analysis (Appendix 1) for the PK sampling methods used in these studies.

One noted limitation of the Population PK analysis (Appendix 1) is also that it failed to include the interim results from Study BRF113771 which arguably contains the most relevant PK data to the submission in terms of using the proposed dose and formulation of dabrafenib (150mg BID, HPMC capsules).

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Pharmacokinetics in healthy subjects

The PK of dabrafenib was not evaluated in healthy subjects. All clinical studies were conducted in subjects with solid tumours, with the majority being subjects with BRAF V600 mutation-positive melanoma.

Comment: The lack of studies involving healthy subjects is in line with the accepted procedures for investigation of anticancer drugs.

4.2.2. Pharmacokinetics in the target population

4.2.2.1. Absorption

4.2.2.1.1. Sites and mechanisms of absorption

Single dose: Study BRF113479 using a single oral dose of 150mg dabrafenib (HPMC capsules), fasted, with an IV microtracer dose, found that absorption of dabrafenib is rapid and nearly complete after oral administration. For the 4 subjects enrolled in the study, the least square mean absolute bioavailability of dabrafenib administered as HPMC capsules was 94.5% (90% CI: 81.3, 109.7), with individual values ranging from 79.3% to 105.9%. Peak concentrations were observed 2 hours post-dose, and decreased thereafter following a bi-exponential decline. In this study, the elimination t½ was longer following oral compared to IV administration, which may suggest prolonged oral absorption. The PK results of this study are outlined in Table 3 below.

Table 3. Summary of PK parameters for plasma dabrafenib, [^{14}C] dabrafenib, and total radioactivity (n=4) following single dose 150mg dabrafenib (HPMC capsules) and IV microtracer dose in Study BRF113479

Parameter[1] (units)	GSK2118436 (Oral)	[^{14}C]GSK2118436 (IV)	Total Radioactivity[2] (IV)
Tmax[3] (hr)	2.0 (2.0, 4.0)	0.25 (0.22,0.32)	0.29 (0.22, 0.33)
Cmax (ng/mL)	2527 (1318, 4845)	3.3 (1.6, 6.8)	4.2 (2.0, 8.6)
AUC(0-t) (ng*hr/mL)	10723 (6989, 16451)	4.1 (3.1, 5.3)	41.1 (21.4, 79.2)
AUC(0-∞) (ng*hr/mL)	10751 (6996, 16523)	4.2 (3.2, 5.4)	43.9 (22.8, 84.5)
t½ (hr)	4.8 (3.0, 7.6)	2.6 (1.8, 3.7)	18.3 (14.7, 22.7)
CL or CL/F (L/h)	14.0 (9.1,21.4)	12.0 (9.2, 15.7)	NA
Vdss (L)	NA	45.5 (28.1, 73.7)	NA

1. Results are presented as geometric mean (95% CI), except for Tmax as median (range).
2. Radioactivity concentrations are expressed as ng equivalents GSK2118436/mL (see also Attachment 4)
3. Tmax for [^{14}C]GSK2118436 and total radioactivity is relative to the time of IV dose administration.

Source: Pharmacokinetic Table 11.4,Table 11.5 and Table 11.6
NA=not applicable

Repeat dose: The interim report for Study BRF113771 presented complete results from Part D of the study, in which the PK of repeat-dose dabrafenib 150mg BID (HPMC capsules) was examined under fasting conditions in 13 subjects. The results are shown in Table 4 below.

Table 4. Summary of plasma dabrafenib PK parameters after single dose (Day 1) and repeat dose (Day 18) administration of 150mg dabrafenib BID as HPMC capsules under fasting conditions in Study BRF113771 (Part D)

Parameter	Day 1 (n=13)	Day 18 (n=11)
Cmax[1] (ng/mL)	2521 (1849, 3435) (55)	2458 (1583, 3818) (73)
tmax[2] (hr)	2.0 (0.5 – 3.1)	1.5 (1.0 – 2.1)
AUC(0-τ)[1] (hr·ng/mL)	9359 (7115, 12311) (48)	6545 (4383, 9771) (61)
AUC(0-24)[1] (hr·ng/mL)	10274 (7610, 13871) (53)[2]	NA
AUC(0-∞)[1,3] (hr·ng/mL)	9626 (7342, 12622) (45)[3]	NA
t½[1] (hr)	4.15 (3.07, 6.51) (53)	2.13 (1.61, 2.81) (43)
Ro[4]	NA	0.73 (0.62, 0.86)
Rt[4]	NA	0.68 (0.57, 0.81)
Rcmax[4]	NA	1.00 (0.80, 1.24)

Source: PK Table 11.5, Table 11.9 and Table 11.10
NA – not applicable, NC – not calculated
Ro – observed AUC(0-τ) accumulation ratio
Rt – time invariance ratio
Rcmax – observed Cmax accumulation ratio

1. Data presented as geometric mean (95% CI) and (CVb %)
2. Median (range)
3. n = 12
4. Reported as geometric least squares mean ratio (90% CI)

Similar PK results were found in Study BRF113468 with single dose dabrafenib 150mg (HPMC capsules), although a longer t½ of 8.4 hours was determined in this study.

Comment: Comparison of Table 3 and Table 4 above reveals that the PK results of single dose dabrafenib 150mg HPMC capsules are generally consistent for Cmax, tmax, AUC and t½ across the two studies. The results for repeat-dose dabrafenib (Table 4) indicate that all parameters (including Cmax, tmax, AUC and t½) are decreased on repeat dosing, likely due to dabrafenib's induction of its own metabolism (see Section 4.2.2.2.8). As dabrafenib is intended for repeat dosing with long-term use, arguably it is the PK of repeat dosing that is clinically relevant rather than following single dose.

4.2.2.2. Bioavailability

4.2.2.2.1. Absolute bioavailability

In Study BRF113479, the absolute bioavailability of dabrafenib administered orally was calculated as 94.5% (90% CI: 81.3, 109.7), calculated in 4 subjects using an oral dose of 150mg (HPMC capsules) and a radio-labelled IV microdose.

Comment: The high oral bioavailability of dabrafenib suggests a low first-pass metabolism.

4.2.2.2.2. Bioavailability relative to an oral solution or micronised suspension

In Study BRF113468, it was found that the relative bioavailability of dabrafenib was higher when orally administered as non-micronised compared to micronised particles, with geometric LS mean ratio (90% CI) of 1.42 (1.06, 1.91) and 1.44 (1.33, 1.83) for Cmax and AUC(0-∞), respectively.

Comment: It is noted that the micronised formulation was used in the development of dabrafenib and clinical trials. The fact that this formulation had reduced bioavailability compared to the non-micronised form has implications as to whether the drug is optimally formulated. However, it is appropriate that the proposed formulation is that which was used in the studies.

4.2.2.2.3. Bioequivalence of clinical trial and market formulations

It was reported that: 'during development, the capsule shell for dabrafenib was changed from a gelatine capsule to an HPMC capsule because of stability issues. It was observed that when gelatine capsules were exposed to high humidity or temperature conditions, there was decreased dissolution over time. Based on *in vitro* dissolution data of the HPMC capsules and bioequivalence comparisons between gelatine and HPMC capsules reported in the literature, it was predicted that clinical exposure would be similar or slightly reduced with HPMC capsules compared to gelatine.' [Study BRF113468].

Comment: It is noted that there were no direct bioequivalence studies between dabrafenib as gelatine and HPMC capsules provided within the submission, with bioequivalence between the two formulations a primary outcome.

In Study BRF113468, although randomisation was not performed across the 2 cohorts, an exploratory comparison of the relative bioavailability of HPMC (Regimen C) versus gelatine capsules (Regimen A) was made. Results indicated that a single 150 mg dabrafenib dose in a HPMC capsule resulted in 1.8-fold higher exposure when compared to administration in a gelatine capsule. The geometric mean exposure [AUC(0-∞)] reported with the HPMC capsule (12120 ng*hr/mL) is generally comparable to the geometric mean AUC(0-∞) of 9980 ng*hr/mL observed after a single dose of 300 mg as a gelatine capsule in Study BRF112680 (FTIH). The highest individual values observed in Study BRF113468 for Cmax and AUC(0-∞) using the HPMC capsules were 5219 ng/mL and 30083 ng*hr/mL, respectively. These single-dose exposures were greater than individual exposures observed in Study BRF112680 at any dose level (up to 300 mg BID). The highest individual Cmax and AUC measured in study BRF112680

was 4464 ng/mL and 16292ng*hr/mL, respectively, following single dose administration of dabrafenib in gelatine capsules.

In the population PK analysis (Appendix 1), these results were confirmed with the HPMC/Gelatine ratio for Cmax and AUC(0-τ) after a single dose of dabrafenib being 1.80 for both parameters, and the ratio at steady state (after repeat dosing) being 1.66 and 2.42 for Cmax and AUC(0-τ) respectively. The HPMC/Gelatine ratio for Ctrough at steady state was 0.98 indicating minimal difference between the formulation types.

Comment: These results indicated that there are potentially clinically relevant differences in the bioavailability of dabrafenib in gelatine capsules used in the earlier clinical trials, and dabrafenib in HPMC capsules used in the latter trials and proposed for registration. The higher bioavailability of the HPMC capsules means that the safety effects of the market formulation may be higher than that observed in the gelatine capsule trials, however, efficacy may also be greater, as was indicated at doses higher than 150mg BID in the FTIH study (see Sections 5.2.2.1 and 6).

A limitation of the submitted data is that no dose-finding studies were specifically performed using dabrafenib HPMC capsules. Rather, the dose selected for further investigation was based on the results of dabrafenib as gelatine capsules (Study BRF112680) and then translated to the same dose in HPMC capsules despite known differences in bioavailability. Furthermore, there appear to be no formal bioequivalence studies performed between the gelatine and HPMC capsules, with that performed in Study BRF113468 only being an exploratory analysis with no randomisation between the cohorts with single dosage, and the analysis from Study BRF13771 comparing the repeat dose PK of dabrafenib as HPMC capsules to historical cohorts using gelatine capsules.

4.2.2.2.4. Bioequivalence of different dosage forms and strengths

No data was presented on this issue.

Comment: It is noted that although the only formulation proposed is for dabrafenib as oral HPMC capsules, two strengths are proposed: 50mg and 75mg, and it does not appear that the bioequivalence of these strengths has been clinically tested.

4.2.2.2.5. Bioequivalence to relevant registered products

Not applicable.

4.2.2.2.6. Influence of food

A substudy of Study BRF112680 found that the administration of dabrafenib with a moderate fat/moderate calorie meal when compared to administration while fasting resulted in a decrease in steady-state Cmax (mean ratio of 0.67 (90% CI: 0.400, 1.13)) and a prolonged tmax (from 2.0 to 3.0 hours), without a significant effect on AUC(0-τ) (mean ratio of 1.06 (90% CI: 0.668, 1.68)).

The food effect was further investigated in Study BRF113468, which found that administration of dabrafenib with a high-fat meal resulted in a decrease in Cmax and AUC of dabrafenib and metabolites, compared to the fasted state. The 90% CI for the ratio of the geometric LS means of Cmax and AUC between fed and fasted regimens were not contained in the equivalence limits of 80 to 125 percent. This suggests that there is a food effect leading to a decrease in exposure of dabrafenib. Absorption of dabrafenib was also slower with the high-fat meal compared to the fasted state with median tmax delayed by 4 hours.

Comment: These results indicate that the PK of dabrafenib is influenced by the presence of food with delayed absorption and reduced bioavailability, and that the drug should be taken while fasting as recommended in the proposed PI.

4.2.2.2.7. Dose proportionality

In Study BRF112680, exposure was observed to increase in proportion to dose after single-dose administration of dabrafenib in gelatine capsules, but less than proportional after repeat dosing. A 2-fold increase in dose (150 mg BID vs. 300 mg BID) resulted in only a 43% increase in dabrafenib AUC(0-τ) at steady state, and no increase in pre-dose concentrations (Cτ). There was a decrease in exposure with repeat dosing of dabrafenib (Day 15 vs. Day 1), possibly due to induction of its own metabolism. In this study, a 2-fold mean increase in the 6-β-hydroxycortisol-to-cortisol urinary ratio, a marker of CYP3A4 activity, was noted after repeat dosing, suggesting induction of CYP3A4 by dabrafenib. The oral clearance (CL/F) of dabrafenib tended to increase with size of the daily dose administered, suggesting greater induction at higher doses.

These results were generally replicated in the interim results from Study BRF113771 which assessed the PK of dabrafenib 75mg BID and 150mg BID with HPMC capsules, however there were differences in the magnitude of the difference between single dose and repeat dosing. These results suggested that with a single dose, a 2-fold increase in dabrafenib resulted in an approximately 3-fold increase in Cmax and AUC(0-∞), while with repeat dosing, a 2-fold increase in dabrafenib resulted in approximately 2.3-fold and 2.1-fold geometric mean plasma dabrafenib Cmax and AUC(0-τ) respectively. However, data collection for this study is not yet complete, and further analysis is planned with the complete results.

As a result of not including data from Study BRF113771 in the analysis, the dose proportionality assessment from the population PK study (Appendix 1) was excluded from consideration in this evaluation.

Comment: The dose proportionality of dabrafenib remains undetermined. On single dosing, available results indicated dose proportionality with gelatine capsules, but exposure was greater than dose proportional with HPMC capsules. On repeat dosing, exposure was less than proportional with gelatine capsules, but approximately dose proportional with HPMC capsules. Further analysis planned on completion of Study BRF113771 will help to clarify this issue, however it would seem prudent to consider the results from this study using HPMC capsules as being more relevant to the proposed formulation.

4.2.2.2.8. Bioavailability during multiple-dosing

The bioavailability of dabrafenib on repeat dosing at the recommended dosage of 150mg BID in HPMC capsules under fasting conditions in Study BRF113771 was Cmax 2458 ng/mL (95% CI: 1583, 3818), tmax 1.5 hrs (95% CI: 1.0-2.1) and AUC(0-τ) 6545 hr*ng/mL (95% CI: 4383, 9771), as described in Table 4. The interim results of this study also found that dabrafenib did not accumulate in the plasma upon repeated dose administration but rather the observed AUC(0-τ) Day 18/Day 1 accumulation ratio was 0.73 (95% CI: 0.62, 0.86), and this decrease in exposure is consistent with dabrafenib's induction of its own metabolism.

These results were consistent with those of Study BRF112680 which found that after repeat dosing, there was no demonstration of dabrafenib accumulation, with a mean accumulation AUC ratio (Day 15 vs. Day 1) of <1.0 for all dose cohorts. The accumulation ratio was 0.824 (95% CI: 0.52, 1.35) for the recommended Part 2 dose of 150mg BID, indicating reduced bioavailability on repeat dosing.

These results were further confirmed in the population PK analysis (Appendix 1) which predicted at a dose of 150mg BID, a steady state to single dose ratio for Cmax of 0.88 and AUC(0-τ) of 0.50. The population PK analysis further estimated the time to reach steady state as 14 days, which is not dependent on dabrafenib half-life, but rather related to CYP enzymes reaching a new steady state due to induction.

Comment: The available results indicate that dabrafenib does not accumulate in the plasma with repeat dosing, but rather there is a decrease in systemic exposure which is consistent with induction of its own metabolism (see Section 4.2.2.4.2). Again, due to the proposed long-term use of dabrafenib, it is therefore more relevant to assess the PK parameters at steady state after repeat dosing, rather than after a single dose.

4.2.2.2.9. Effect of administration timing

The PK analysis of Study BRF112680 found there was no accumulation of dabrafenib with once daily, BID or TID dosing. In Part 1 of this study, the 300 mg daily total dose of dabrafenib was administered as either 100 mg TID or 150 mg BID in order to explore which schedule would maintain exposure better over the dosing interval. On the basis of the pre-dose concentration (Cτ) reported in all subjects (n=14-18), exposure was similar between TID and BID regimens, with Day 8 and Day 15 geometric means of 87.8 and 141 ng/mL, respectively, for TID dosing vs. 80.2 and 96.1 ng/mL, respectively, for BID dosing.

As discussed in Section 4.2.2.2.6, dabrafenib absorption and bioavailability is decreased in the presence of food, and should be administered fasted.

Comment: Based on the results form Study BRF112680, administration BID would seem reasonable. However, once again, this study was conducted using dabrafenib as gelatine capsules, and no studies have examined dabrafenib as HPMC capsules administered at frequencies other than BID.

4.2.2.3. Distribution

4.2.2.3.1. Volume of distribution

In Study BRF113479, the Volume of distribution at steady state (Vdss) was calculated for [^{14}C]dabrafenib after IV administration as 45.5L, consistent with total body water. In the population PK analysis (Appendix 1) the Vc/F (apparent volume of central compartment) was estimated at 70.3 L, and the Vp/F (apparent volume of peripheral compartment) was estimated at 154 L.

Comment: The Vdss of dabrafenib indicates that the drug does not accumulate in the tissues.

4.2.2.3.2. Plasma protein binding

In vitro studies were reported to have found dabrafenib and its metabolites to be highly protein bound in human plasma, with dabrafenib, hydroxy-dabrafenib, carboxydabrafenib, and desmethyl-dabrafenib, 99.7, 96.3, 99.5, and 99.9% bound to plasma proteins, respectively.

In vitro studies also reported that dabrafenib was a highly permeable compound based on the Biopharmaceutics Classification System (BCS).

4.2.2.3.3. Erythrocyte distribution

In the radio-labelled Study BRF113463, mean total radioactivity in plasma and blood PK profiles were generally parallel, with mean blood:plasma ratios of total radioactivity ranging from 0.48 to 0.69 from 0.5 hours through 216 hours post-dose. These results suggest minimal association of radioactivity (dabrafenib and metabolites) with red blood cells.

4.2.2.3.4. Tissue distribution

Pre-clinical studies were reported to show that dabrafenib and its metabolites have different lipophilicity which may affect distribution to different tissues. The levels of dabrafenib, carboxy-dabrafenib and hydroxy-dabrafenib in xenograft tumour homogenate were reported to be consistently lower than those in plasma, whereas levels of desmethyl-dabrafenib were higher in

xenograft tumour than in plasma (although desmethyl-dabrafenib formation from carboxy-dabrafenib upon tissue sample processing could not be entirely ruled out).

Based on preclinical data, it was reported that dabrafenib and desmethyl-dabrafenib may cross intact blood brain barrier. It was reported that distribution across an intact blood-brain barrier was found to be minimal in preclinical studies based on single dose data in the rat, pig and mouse. However, following repeat dosing in mice, the brain to plasma AUC(0-t) ratios for parent, carboxy-dabrafenib, and desmethyl-dabrafenib were reported to be 4.25, 0.14, and 36, after correcting for protein binding, suggesting that desmethyl-dabrafenib and to a lesser extent, dabrafenib, may penetrate intact brain tissue. Hydroxy-dabrafenib was not reported to be detected in the brain. Dabrafenib was found to be active in subjects with BRAF V600 mutation positive melanoma with brain metastases in Study BRF113929 (see section 7.1.2.2). Distribution of dabrafenib or its metabolites to the brain may be secondary to the disruption of the blood brain barrier observed with brain metastases, or dabrafenib or its metabolites may be able to cross an intact blood brain barrier.

Comment: One of the main claims of dabrafenib is that it is efficacious in the treatment of metastatic melanoma to the brain. Although this statement would seem correct, the mechanism of distribution to the brain remains unknown.

4.2.2.4. Metabolism

4.2.2.4.1. Interconversion between enantiomers

No data was provided – as described in Section 4.2.1, it was reported in pre-clinical studies that dabrafenib mesylate has no potential for optical or geometrical isomerisation.

4.2.2.4.2. Sites of metabolism and mechanisms / enzyme systems involved

As reported in the [sponsor's] non-clinical summary, the biotransformation pathway of dabrafenib in humans is as follows:

'Following oral administration of dabrafenib, it is absorbed into the bloodstream and its metabolism to hydroxy-dabrafenib (GSK2285403) is mediated mainly by hepatic CYP2C8 and CYP3A4. Hydroxy-dabrafenib circulates in blood and is metabolised to carboxy-dabrafenib (GSK2298683) in liver by CYP3A4 (alternatively, a small amount of hydroxy-dabrafenib is glucuronidated). Carboxy-dabrafenib circulates until it is eliminated slowly via the urine or bile. Following biliary secretion, carboxy-dabrafenib is decarboxylated in the gut to form desmethyl-dabrafenib (GSK2167542), which is either excreted in faeces or reabsorbed back into the bloodstream. Finally, desmethyl-dabrafenib is metabolised mainly by CYP3A4 to minor oxidative metabolites (M26, M28, M29, M30 and M31)'.

Comment: From this metabolic pathway, it can be predicted that changes in induction or inhibition of the CYP3A or CYP2C enzymes may have an effect on the PK of dabrafenib and its metabolites.

This metabolic pathway was supported by the radio-labelled study 11DMM013, however, it was noted in this study that 1 out of 4 subjects was considered exceptional with metabolite profiles qualitatively and quantitatively different from the other 3 subjects. The implications of these differences were not discussed or explored further.

Comment: Inter-individual differences in the metabolism of dabrafenib may be of clinical significance in light of the clinical activity and long half-lives of the metabolites. This may be an area that warrants further research.

In Study BRF113479, it was found that dabrafenib is metabolised extensively, with the fraction of AUC(0-∞) of parent compared to total radioactivity after IV administration of [^{14}C]dabrafenib being 9.6%.

As discussed in previous sections (4.2.2.2.7 and 4.2.2.2.8), dabrafenib induces its own metabolism. An *in vitro* study to evaluate the effect of dabrafenib on messenger RNA (mRNA) levels of CYP genes in cultured human hepatocytes was reported to show that at 30 μM dabrafenib, maximal increases in CYP2B6 and CYP3A4 mRNA levels to a mean ratio ('dabrafenib treated' over control) of 32 and 30 were observed. This, respectively, corresponded to 320% and 150% increases relative to their prototypic inducers phenytoin (CYP2B6) and rifampicin (CYP3A4).

Comment: Extensive metabolism of dabrafenib including contribution from enzyme induction highlights the importance of metabolism in the clearance of dabrafenib. Therefore, any processes or interactions which affect enzyme metabolic activity are likely to have an impact on the PK of dabrafenib.

4.2.2.4.3. Non-renal clearance

In Study BRF113479, the calculated IV clearance of 12.0 L/h was low and approximately 7% of liver blood flow (where liver blood flow is 81 L/h), indicating a low hepatic clearance for dabrafenib relative to liver blood flow.

Comment: Low hepatic clearance is consistent with a large metabolic clearance of dabrafenib.

4.2.2.4.4. Metabolites identified in humans

· **Active metabolites**

Three pharmacologically active circulating metabolites of dabrafenib were reported to have been observed in human in vivo studies (hydroxy-, carboxy- and desmethyldabrafenib, or GSK2285403, GSK2298683 and GSK2167542 respectively), representing sequentially formed products of oxidation and decarboxylation. The potency of these metabolites relative to parent on a ng/mL basis was reported to be approximately 2, 1/24, and 1/8 for hydroxy-, carboxy- and desmethyldabrafenib, respectively, based on results on an *in vitro* protein-shifted cellular pERK assay in SKMEL28 cell lines and a cell proliferation assay in Colo205 cell lines. It was reported that based on *in vitro* potency, pharmacology and PK characteristics, hydroxy- and desmethyl-dabrafenib likely contribute to clinical activity, while carboxy-dabrafenib is thought to be essentially inactive.

In radio-labelled Study BRF113463, using the geometric mean plasma AUC(0-∞) ratios of dabrafenib to total plasma radioactivity, the percentage of total radioactivity in the form of parent compound was approximately 11%. The metabolites GSK2285403, GSK2298683 and GSK2167542, accounted for approximately 8%, 54% and 3% of plasma radioactivity, respectively (corrected for molecular weight). Therefore, the majority (76%) of plasma radioactivity was accounted for in the form of dabrafenib and known circulating metabolites.

Comment: It is agreed that the three main circulating metabolites of dabrafenib (hydroxy-, carboxy- and desmethyl-dabrafenib) have sufficient potency and are present at exposures which suggest they may contribute to the clinical activity of the parent drug.

· **Other metabolites**

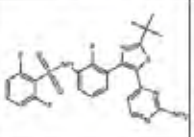
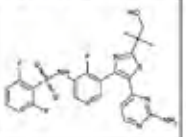
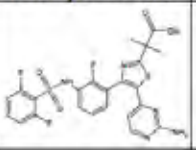
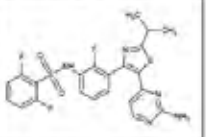
In humans following a single dose, 4 minor metabolites which have not been detected in any nonclinical species, were reported to be observed at mean concentrations of less than 10% of the drug-related material in plasma.

4.2.2.4.5. Pharmacokinetics of metabolites

The characteristics of dabrafenib and its metabolites, hydroxy- (GSK2285403), carboxy- (GSK2298683) and desmethyl-dabrefenib (GSK2167542), are presented in Table 5 below. The

PK results following administration of dabrafenib 150mg BID at single and repeat-dosages are drawn from Studies BRF113468 and BRF113683 (BREAK-3) respectively.

Table 5. Characteristics of dabrafenib and its metabolites

Analyte	Dabrafenib	Hydroxy-Dabrafenib	Carboxy-Dabrafenib	Desmethyl-Dabrafenib
Structure				
Clinical Pharmacokinetics				
Tmax (SD) (hr)	2.0 (1.0, 4.0)	4.0 (2.0, 10.0)	10.0 (6.0, 24.0)	36.2 (10.0, 72.2)
t1/2 (SD) (hr)	8.4 (113)	9.7 (85)	20.9 (29)	22.2 (43)
AUCm/p Ratio, SD	NA	0.9 (23)	7.0 (71)	0.5 (65)
Cmax, RD (ng/mL)	1478 (37)	1009 (36)	6153 (33)	347 (40)
AUC(0-τ), RD (ng*hr/mL)	4341 (38)	4067 (38)	51485 (39)	3068 (35)
Cτ, RD (ng/mL)	26.1 (119)	46.3 (124)	2805 (46)	235 (45)
AUCm/p Ratio, RD	NA	0.9	11.2	0.7
Metabolism Data				
Metabolism	CYP2C8, CYP3A4	CYP3A4, glucuronidation	Biliary, Urinary Excretion	CYP3A4
Effect of CYP3A4 inhibition	↑ (57%)	↑ (48%)	↓ (33%)	↑ (61%)
Protein Binding (%)	99.7	96.3	99.5	99.9
Pharmacology Data (reported as IC50/gIC50 [nM] and fold relative to parent)				
BRAFV600E	0.65 (NA)	1.9 (2.9-fold)	16.6 (25.5-fold)	1.1 (1.7-fold)
pERK	9 (NA)	7 (0.8-fold)	156 (17.3-fold)	8 (0.9-fold)
Colo205 (10% FBS)	6 (NA)	23 (3.8-fold)	320 (53.3-fold)	23 (3.8-fold)
Colo205 (70% Human Serum)	518 (NA)	401 (0.8-fold)	11544 (22.3-fold)	6167 (11.9-fold)

SD=Single Dose (BRF113468); RD=Repeat Dose (BRF113683); Metabolism Data (In vitro data [m2.4, Section 3.4.3 and Section 3.3.1] and Study BRF113771); Pharmacology Data (m2.4, Section 2.1.1, m2.6.2, Section 2.2.1, Section 2.2.5, Section 2.2.6); FBS=fetal bovine serum; Clinical PK parameters are reported as geometric mean (%CVb), with the exception of Tmax which is reported as median (range).

As detailed in Table 5, it can be seen that the PK profile of hydroxy-dabrafenib appears to be formation-rate limited and thus the terminal phase parallels that of parent. Carboxy- and desmethyl-dabrafenib exhibited a prolonged half-life relative to dabrafenib. It has been hypothesised that the long half-life observed with desmethyl-dabrafenib is likely to contribute to efficacy at the end of the 12-hr dosing interval.

The single dose PK of the main dabrafenib metabolites were evaluated in Study BRF113468, with a single dose of 150mg (HPMC capsules) over a sampling period of 96 hours. This sampling period was longer than that used during the FTIH study BRF112680, where samples were collected only up to 24 hours after single dose administration, and due to the long t½ of the metabolites allowed for better determination of metabolite PK parameters. From this study, hydroxy-darbafenib appears to be formation rate-limited, as the observed t½ was similar to the parent. Carboxy- and desmethyl-dabrafenib displayed longer half-lives relative to parent, and the half-lives of these 2 metabolites were similar (approximately 20 hours). The tmax values of the metabolites were delayed relative to parent and consistent with the order of sequential metabolism observed *in vitro*. Following single dose administration, the metabolite to parent AUC ratios were 0.9, 7.0 and 0.5 for hydroxy-, carboxy- and desmethyl-dabrafenib, respectively. After repeat dosing, the pharmacologically active metabolites had metabolite to parent AUC0-t ratios of 0.9, 11.2 and 0.7 for hydroxy-, carboxy- and desmethyl-dabrafenib, respectively.

Comment: These results indicate that metabolite to parent AUC ratios were similar after single- and repeat-dosing for hydroxy- and desmethyl-dabrafenib, but greater after repeat dosing for carboxy-dabrafenib, possibly indicating less impact on the latter from auto-induction of CYP3A4 metabolism.

The above results supported that of Study BRF112680, which found that after repeat-dose administration of 150 mg BID dabrafenib (gelatine capsules), exposure for hydroxy-, carboxy- and desmethyl-dabrafenib relative to parent was 0.8, 19, and 1.0, respectively. Exposure for all metabolites showed a less than proportional increase with dose on Day 15. Carboxy- and desmethyldabrafenib had long terminal half-lives and were found to accumulate with repeat dosing, reaching a steady state by Day 8.

The interim results of Study BRF113771 using HPMC capsules again supported the above findings, with delayed appearance of all dabrafenib metabolites in plasma with respect to parent after a single dose of dabrafenib. Geometric mean (95% CI) metabolite to parent AUC(0-t) ratios were 0.56 (0.448, 0.686), 9.62 (7.54, 12.3), and 0.741 (0.447, 1.23) for hydroxy-, carboxy-, and desmethy-dabrafenib, respectively. The PK of hydroxy-dabrafenib most closely mirrored that of dabrafenib with a delay of 1 hour for tmax, t½ was similar, and there was no accumulation or change in Cmax after repeat dose administration. In contrast, the appearance of carboxy- and desmethyl-dabrafenib was delayed with respect to hydroxy-dabrafenib after a single dose of dabrafenib, with longer tmax and t½, and plasma accumulation following repeated BID administration.

Population analysis was performed on covariates affecting the PK of dabrafenib metabolite pre-dose concentrations (Cτ) following repeat dosing of dabrafenib at 150mg BID. This found that for hydroxy-dabrafenib followed a similar pattern to dabrafenib, with a greater degree of inter-individual variability due to the relatively short t½, and there were higher trough concentrations associated with increasing body weight and with CYP3A inhibitor co-administration (31% higher for hydroxy-dabrafenib). Population estimates of pre-dose concentrations (Cτ) were higher for carboxy- and desmethyl-dabrafenib compared to hydroxy-dabrafenib and dabrafenib. Carboxy- and desmethyl-dabrafenib also had less inter-individual and residual variability, higher trough concentrations associated with age (41% and 42% higher with Age≥75 years, for carboxy- and desmethyl-dabrafenib respectively), lower trough concentrations associated with gelatine capsule shell (12% and 19% lower with gelatine shell for carboxy- and desmethyl-dabrafenib respectively), and there were lower carboxy-dabrafenib (14% lower) trough concentrations associated with CYP3A inducer co-administration.

Comment: The PK parameters of dabrafenib metabolites are consistent with the metabolic pathway outlined in Section 4.2.2.4.2. Overall it appears that hydroxy- and desmethyl-dabrafenib contribute to the clinical activity of dabrafenib due to the relative potency of the former and the long half-life of the latter. Although carboxy-dabrafenib is present at higher concentrations and has a long half-life, it is not thought to contribute to clinical activity due to its low potency.

In line with the contribution of dabrafenib metabolites to clinical activity, it is anticipated that they also contribute to the adverse events associated with dabrafenib use. One instance of this is the contribution of dabrafenib metabolites to QT prolongation, as is discussed in Section 8.5.5.

4.2.2.4.6. Consequences of genetic polymorphism

No data was provided with this submission.

Comment: Although none of the submitted studies specifically examined this issue, again it may be of clinical relevance due to the extensive metabolism of dabrafenib and the potential impact of differences in enzyme activity.

4.2.2.5. Excretion

4.2.2.5.1. Routes and mechanisms of excretion

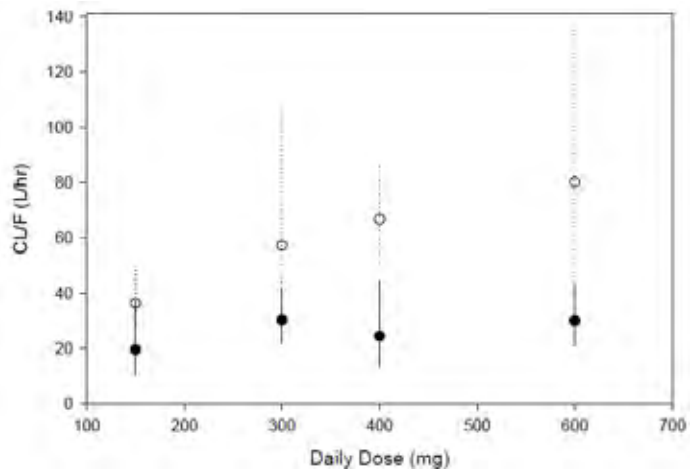
In Study BRF113463, following a single 95 mg oral dose of 14C-dabrafenib suspension, total recovery of radioactivity in urine and faeces was high (93.8%, range 88.4%-100%), with the majority recovered in the faeces (71.1%). However, as the oral bioavailability of dabrafenib in

suspension is unknown, it is unclear what proportion of the total amount excreted in faeces is due to unabsorbed drug or biliary excretion of dabrafenib and/or metabolites. Urine recovery of radioactive dose was 22.7%. The majority of radioactivity was excreted by 96 hours.

In Study BRF113479, after single dose administration, the plasma clearance of dabrafenib was 14.0 L/hr (95% CI 9.1, 21.4) following oral administration and was 12.0 L/hr (95% CI 9.2, 15.7) after IV administration.

In Study BRF112680, oral clearance of dabrafenib was found to increase with both repeat-dosing and with increased dose, indicating induction of its own metabolism with greater induction at higher dosages, as illustrated in Table 6 below.

Table 6. Dabrafenib oral clearance (CL/F) geometric mean (symbols) and 95% confidence intervals (bars) by total daily dose on Day 1 (closed circles) and Day 15 (open circles), Dose escalation: Part 1, Study BRF112680



It was reported in the Clinical Pharmacology Summary in Module 2.7.2 of the submission that the CL/F of dabrafenib after repeat dosing at 150mg BID was measured at 35 L/hr in Study BRF113683 (BREAK-3), although no reference to this could be found in the study CSR.

In the Population PK study (Appendix 1) total apparent oral clearance (CL/F) of dabrafenib was estimated using a non-inducible CL_0/F of 17.0 L/hr and an inducible CL_{ind}/F which increased with time and reached steady state following administration of dabrafenib 150mg BID (HPMC capsules) of 17.3 L/hr. Therefore, the predicted total apparent oral clearance at steady state was 34.3 L/hr reached after 14 days of dosing.

Comment: Total dabrafenib clearance appears to depend on both non-inducible and inducible (enzyme mediated) clearance, the latter reaching steady state after 14 days of dosing. As the proposed usage of dabrafenib is for long-term use, it is the total clearance after repeat dosing (following enzyme induction) that is clinically relevant and should be included in the PI, rather than clearance following a single dose of dabrafenib.

In Study BRF113479 terminal half-life in 4 subjects following IV microdose of dabrafenib was 2.6 hrs (range 1.8-3.7). Median terminal half-life after oral administration of single dose dabrafenib 150mg (HPMC capsules) in these same subjects was 4.8 hrs (range 3.0-7.6), potentially due to a prolonged absorption phase after oral administration. In Study BRF113468, the median t½ in 13 subjects following a single dose of oral dabrafenib 150mg (HPMC capsules) was 8.4 hours (range 2.4-38.2).

4.2.2.5.2. Mass balance studies

The primary objective of Study BRF113463 was to determine the total recovery and relative excretion of radioactivity in urine and faeces after a single, oral 95 mg suspension dose of

[^{14}C]dabrafenib containing approximately 80 µCi of radioactivity in subjects with BRAF mutant solid tumours. Mean total recovery of the radioactive dose in the 4 subjects enrolled in the study was 93.8% (range of 88.4 to 100%) with faecal excretion being the predominant route of elimination accounting for 71.1% of the oral dose. Urine recovery accounted for 22.7% of the radioactive oral dose. Association of radioactivity with red blood cells was minimal. Of the circulating plasma radioactivity, dabrafenib and its metabolites (including GSK2285403, GSK2298683, and GSK2167542), quantified using validated liquid chromatography/mass spectrometry (LC/MS) methods, accounted for approximately 11%, 8%, 54% and 3% of the plasma radioactivity AUC(0-∞), respectively (total of approximately 76%).

Comment: From this study, the majority (93.8%) of dabrafenib is excreted in faeces and urine within 240 hours of dosing.

4.2.2.5.3. Renal clearance

In Study BRF112680, an exploratory analysis in 5 subjects dosed at 200mg BID revealed that the median recovery of drug-related material (dabrafenib and 3 metabolites: hydroxy- , carboxy- and desmethyldabrafenib) in urine after repeat dosing was 4.07% of the dose (range 2.92-9.88%).

As described above, in the radio-labelled Study BRF113463 following a single, oral 95 mg suspension dose of [14C]dabrafenib containing approximately 80 µCi of radioactivity in subjects with BRAF mutant solid tumours, urine recovery accounted for 22.7% of the radioactive oral dose.

Comment: These results indicate that the renal excretion of dabrafenib and its metabolites is low.

4.2.2.6. Intra- and inter-individual variability of pharmacokinetics

In the Population PK study (Appendix 1) the PK of dabrafenib was characterised by high inter-individual variability, with CV of 57%, 53%, 99%, and 160% for CL0/F, Vc/F, Q/F and Ka, respectively. CV of the proportional portion of the residual error was 53%. In this Population PK study, intra-occasion variability was excluded from the final model as most of the included studies only applied sparse sampling methods.

Comment: The PK of dabrafenib shows high inter-individual variability, however the intra-individual variability does not appear to have been systematically investigated.

4.2.3. Pharmacokinetics in other special populations

4.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

Subjects with severe hepatic impairment were excluded from all studies presented in the submission. The Population PK analysis (Appendix 1) found no association between mild hepatic impairment (classified as ULN < BILI < 1.5*ULN or BILI < ULN and BAST > ULN) found in 68/595 subjects and PK parameters.

However, it is stated in the Summary of Clinical Pharmacology that: 'Dabrafenib is metabolized by CYP enzymes, therefore it is anticipated that hepatic impairment could alter dabrafenib disposition. A study in subjects with hepatic impairment is being conducted by the NCI (BRA115947).'

Comment: Although no association was found in the population PK analysis between mild hepatic impairment and dabrafenib PK parameters, no subjects with moderate or severe hepatic impairment were included in the analysis. In light of dabrafenib's primary mode of clearance being via metabolism by CYP enzymes, it is anticipated that impaired hepatic function may impact on dabrafenib metabolism and increase its exposure. The results of the study in progress may assist in clarifying this issue.

4.2.3.2. Pharmacokinetics in subjects with impaired renal function

Subjects with severe renal impairment were excluded from all studies presented in the submission. The Population PK analysis (Appendix 1) found no association between mild (90 > GFR > 60 mL/min/1.73m^2) or moderate (60 > GFR > 30 mL/min/1.73m^2) renal impairment, found in 233 (39.2%) and 30 (5.0%) subjects respectively, and PK parameters. It was noted that a study in subjects with severe renal impairment is currently being conducted.

Comment: As with hepatic impairment above, although no association was found in the population PK analysis between mild or moderate renal impairment and dabrafenib PK parameters, as the number of subjects with moderate impairment were low and there were no subjects with severe renal impairment, the effect of impaired renal function on dabrafenib PK cannot definitively be commented on. However, in line with the finding of low renal excretion of dabrafenib and its metabolites in Study BRF113463, where 22.7% of a radioactive dose was recovered in the urine, renal impairment is less likely to have a clinically relevant effect on the PK of dabrafenib. Again, the results of the study in progress will assist in clarifying the issue.

4.2.3.3. Pharmacokinetics according to age

In the Population PK analysis (Appendix 1), age (categorised as ≤65 years, >65 to 75 years, inclusive, and >75 years) was not found to impact on PK parameters.

4.2.3.4. Pharmacokinetics related to genetic factors

No data was provided with this submission.

Comment: Due to the high metabolic clearance of dabrafenib, genetic factors may have a significant impact in dabrafenib PK.

4.2.3.5. Pharmacokinetics according to gender

In the Population PK analysis (Appendix 1), gender was a significant predictor of dabrafenib exposure, with oral clearance in female subjects being 0.91 (95%CI: 0.87 - 0.95) of that in males. Following administration of 150 mg BID (HPMC capsules), dabrafenib Cmax, AUC(0- τ), and Ctrough were respectively 3%, 9%, and 26%, higher in female subjects relative to male subjects. This effect was considered small however, and not clinically significant.

Comment: It is agreed that the effect of gender on dabrafenib exposure, although statistically significant, is small and not clinically relevant, and thus differential dosing according to gender is not warranted.

4.2.3.6. Pharmacokinetics according to weight

In the Population PK analysis (Appendix 1), weight was identified as a significant covariate on total CL/F, Vc/F, and Q/F. However, as all PK parameters in a typical subject with low (50 kg) or high (140 kg) body weight were predicted to be within 20% of the value of a typical 80 kg subject, this effect was not considered by the Sponsor to be clinically relevant.

Comment: It was noted in Appendix 1 that the difference in PK parameters between subjects with low (50 kg) and high (140 kg) body weight is of the order of 32-52%. This difference may be clinically significant, and may warrant further investigation or monitoring.

4.2.3.7. Pharmacokinetics according to ethnicity

Across the studies, most subjects recruited were White. In the population PK analysis, only 9 (1.5%) subjects were not Caucasian, and only 21 (3.5%) subjects were Hispanic or Latino, therefore race and ethnicity covariates were not explored.

It was reported in the summary of clinical pharmacology that based on the data available to date, there is potential for inter-ethnic differences to exist both in CYP-mediated oxidation steps and in transporter driven processes involved in hepatic uptake and excretion of drug related material into the gastrointestinal tract. Should such differences exist, exposure to dabrafenib and its metabolites may vary between ethnic groups; any clinical consequences of this cannot be predicted at this point.

Comment: Due to the PK of dabrafenib in ethnic groups other than Caucasian being unknown, use of dabrafenib in these groups should be made with caution. This is particularly important in light of the large proportion of dabrafenib eliminated by metabolism, and the known variation in enzymic activity that occurs between different ethnic groups.

4.2.4. Pharmacokinetic interactions

4.2.4.1. Pharmacokinetic interactions demonstrated in human studies

· **CYP3A4 activity:**

In Study BRF112680, the mean Day 15/Day 1 ratio of β-hydroxycortisol to cortisol was calculated to be 1.98 (95% CI: 1.75, 2.2.3) indicating induction of CYP3A4 activity by dabrafenib. Further investigation of the effect of dabrafenib on midazolam (a CYP3A4 probe) in this study found that co-administration resulted in decreased midazolam exposure (mean Cmax and AUC(0-∞) (90% CI) ratio of 0.39 (0.24, 0.63) and 0.26 (0.21, 0.32), respectively) and a shorter midazolam half-life compared to when midazolam was administered alone, confirming induction of CYP3A4 activity.

Comment: These results indicate that dabrafenib is an inducer of CYP3A4 activity, and this could be one mechanism of dabrafenib's induction of its own metabolism.

Study BRF113771 is an ongoing study investigating the effects of dabrafenib (as a perpetrator inducing CYP2C) on the PK of warfarin; the effect of the CYP3A4 inhibitor ketoconazole on the PK of dabrafenib (as a victim); and the effect of the CYP2C8 inhibitor gemfibrozil on the PK of dabrafenib (as a victim). Currently only interim results on the effect of ketoconazole are available. These suggest that administration of ketoconazole 400mg daily causes an increase in systemic exposure to dabrafenib 75mg BID HPMC capsules, with increases in Cmax and AUC(0-τ) of 26% and 57% respectively, which is consistent with inhibition of CYP3A4-mediated metabolism of dabrafenib. The net effect on exposure to metabolites of dabrafenib is dependent on the effects of CYP3A4 inhibition on formation and elimination of the metabolite, with increases observed in the systemic exposure of hydroxy-dabrafenib (GSK2285403) and desmethyl-dabrafenib (GSK2167542), and decreased exposure to carboxy-dabrafenib (GSK2298683).

Comment: These results indicate that dabrafenib exposure is increased in the presence of a CYP3A4 inhibitor, with variable effects on exposure to metabolites. These interim results need to be confirmed on completion of the study, and assessed in addition to the findings on the effect of CYP2C induction by dabrafenib or inhibition by gemfibrozil.

4.2.4.2. Clinical implications of in vitro findings

As is described in the Nonclinical overview in Module 2.4 of the submission:

It was reported that estimates based on *in vitro* studies indicated that CYP2C8 contributed approximately 50 to 67% and CYP3A4 contributed 24 to 50% to the oxidative metabolism of dabrafenib, with minor contributions from CYP2C9 and 2C19. Both hydroxy-dabrafenib and desmethyl-dabrafenib were reported to be metabolised mainly by CYP3A4, while carboxy-dabrafenib was not oxidatively metabolised, but instead underwent decarboxylation to form desmethyl-dabrafenib. Therefore, co-administration with known strong inhibitors or inducers

of CYP2C8 and CYP3A4 will likely alter the pharmacokinetics of dabrafenib and its circulating metabolites, and this has been demonstrated clinically for CYP3A4.

It was also reported that dabrafenib was shown to be a substrate for human P-glycoprotein (Pgp) and murine breast cancer resistance protein 1 (Bcrp1) efflux transporters *in vitro*. However, given the high oral bioavailability (94.5%) and high metabolic clearance of dabrafenib, these efflux transporters appear to have minimal impact on its bioavailability and elimination. Thus, the potential impact of Pgp and/or Bcrp inhibitors on the elimination of dabrafenib was reported to be low, although they could affect the tissue distribution of dabrafenib or its metabolites, most notably brain tissue penetration. The potential effect of Pgp or Bcrp inducers was not commented on.

In vitro, dabrafenib and its metabolites were reported to variably demonstrate moderate inhibition of CYP2C8, 2C9, 2C19 and 3A4 in human liver microsomes. Dabrafenib was also reported to induce human CYP3A4 and CYP2B6 in human hepatocytes. The potential for dabrafenib to interact with drugs that are sensitive substrates of CYP2C8, CYP2C9 and CYP2C19 was minimal as calculated using a mechanistic static mathematical model, however, the predicted net effect of dabrafenib on sensitive substrates of CYP3A4 was CYP3A4 induction and a consequent decrease in substrate exposure, as was observed clinically with midazolam.

Comment: The preclinical findings indicate that dabrafenib and its metabolites are substrates for CYP3A4, CYP2C8, Pgp, and Bcrp1. Therefore, it could be anticipated that any alteration to these enzymes or transporters may affect the PK of dabrafenib. In addition, dabrafenib was found pre-clinically to demonstrate moderate inhibition of CYP2C8, 2C9, 2C19, and 3A4, as well as induce CYP3A4 and CYP2B6, and thus may alter the PK of other drugs that are sensitive substrates for these enzymes. The results of further clinical studies are needed to better characterise these interactions.

Several drug classes are inducers or inhibitors of CYP3A or CYP2C8, or substrates of these enzymes that may be used in the target patient population of subjects with advanced or metastatic melanoma. Such drugs include certain antibiotics, antifungals, antidepressants, anticonvulsants, and antiarrythmics. Although use of these drugs was excluded in the clinical trials, there is potential for their co-administration in clinical practice and thus caution is warranted.

4.3. Evaluator's overall conclusions on pharmacokinetics

The PK analysis has been confounded somewhat due to the change in formulation of dabrafenib from gelatine to HPMC capsules part-way through the clinical trial process. Therefore, the studies presented contained a proportion that used either of the two formulation types. A significant issue is that there does not appear to have been any formal and direct clinical bioequivalence studies performed across the two formulations. The only information on bioequivalence contained within the submission was an exploratory analysis in Study BRF113468, and the population PK analysis (Appendix 1). Moreover, these analyses found that the two formulations were not bioequivalent, with a single 150 mg dabrafenib dose in a HPMC capsule resulting in 1.8-fold higher exposure compared to administration in a gelatine capsule, and similar results at steady state.

It is acknowledged that the overall effect of the change in formulation from gelatine to HPMC capsules was an increase in bioavailability, therefore the expected effect would be an increase in clinical activity without significant impact on tolerability, since a MTD was not reached during the original dose-finding study. However, it is a limitation that the recommended dabrafenib dose of 150mg BID determined in the dose finding study using gelatine capsules was continued as the recommended dose using HPMC capsules without any further dose-finding studies with this new formulation. In addition, there have been no bioequivalence studies performed on the

two proposed dosage strengths of 50mg and 75mg HPMC capsules. Throughout this CER, more emphasis has been placed on the results drawn from the studies using HPMC capsules, as is proposed for registration, where these were available.

From the results of the presented PK studies, it is concluded that dabrafenib is well absorbed when administered orally with a high bioavailability of 94.5%, a tmax of around 2 hours, and a terminal half-life of between 4.8 to 8.4 hours. There was no difference in exposure with BID or TID dosing, and thus BID dosing would seem appropriate. There was delayed absorption and bioavailability when dabrafenib was administered with food, and thus the recommendation to administer while fasted is warranted. Dabrafenib is highly plasma protein bound, and appears to cross blood brain barrier on repeat dosing and thus have a potential clinical effect on brain metastases.

Dabrafenib has been found to induce CYP enzymes and, via the induction of CYP3A4 (and possibly CYP2C8), it induces its own metabolism. Therefore there is no accumulation of dabrafenib on repeat dosing, but rather steady state to single dose ratios for Cmax and AUC are of the order of 0.5 to 0..88 across the various studies. Similarly, the degree of increased exposure with increasing dabrafenib dose is diminished over time, although the extent of dose-proportionality remains uncertain as differences were observed between the different capsule formulations (gelatine or HPMC).

94% of dabrafenib was found to be excreted in urine or faeces within 240 hours of dosing. Elimination of dabrafenib is primarily by metabolism, with limited contribution from biliary and renal clearance. Therefore, the effect of enzyme induction is significant on total body clearance of dabrafenib. The population PK analysis calculated a non-inducible clearance (from all mechanisms) of 17.0 L/hr and an inducible clearance that increased with time and reached a steady state of 17.3 L/hr following administration of dabrafenib 150mg BID (HPMC capsules). Therefore, the predicted total apparent oral clearance at steady state was 34.3 L/hr reached after 14 days of dosing. Due the proposed long-term use of dabrafenib in the treatment of melanoma patients, it is arguably the PK at steady state after repeat dosing that is clinically relevant and should be stated within the product information.

Dabrafenib is sequentially metabolised to form the active metabolites hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib. In particular, hydroxy- and desmethyl-dabrafenib are thought to contribute to the clinical activity (and adverse event profile) of dabrafenib. The PK of hydroxy-dabrafenib parallels that of the dabrafenib, whereas carboxy- and desmethyl-dabrafenib exhibit longer half-lives.

High inter-individual variability was observed in the PK of dabrafenib. On population PK analysis, the only covariates found to significantly impact on the PK parameters were gender and body weight (using a full model approach with all covariate-parameter relationships entered simultaneously), neither of which was considered by the Sponsor to be clinically relevant. However, the opinion of this evaluator is that body weight, for which the difference between subjects with low and high weight was found to be of the order of 32-52%, may be a relevant factor. There was no observable effect of age on the PK of dabrafenib.

The PK of dabrafenib has not been investigated in subjects with severe hepatic or renal impairment as such subjects were excluded from the clinical trials completed to date. However, based on the known metabolic and excretion pathway of dabrafenib with the majority being cleared by CYP enzymes, it is anticipated that hepatic impairment is likely to impact on the PK of dabrafenib and potentially increase its exposure. Therefore, caution is required in the administration of dabrafenib to subjects with hepatic impairment. Conversely, due to low renal excretion (22.7% of a radioactive oral dose), renal impairment is less likely to impact on dabrafenib PK. The results of studies in patients with hepatic and renal impairment currently being conducted will help to clarify these issues.

Due to the predominance of metabolism in the clearance of dabrafenib (over renal and biliary clearance), attention needs to be paid to mechanisms and interactions which may impact on metabolic pathways. Specifically, drugs or factors that lead to induction or inhibition of CYP enzymes (in particular CYP3A4 and CYP2C8) may impact on the PK of dabrafenib and its metabolites. This has been shown clinically with interactions seen between dabrafenib and midazolam and ketoconazole, while the results of interaction with warfarin and gemfibrozil are pending. However, other specific factors that may cause differences in enzyme function such as racial and genetic differences have not been investigated, and therefore dabrafenib should also be used with caution in ethnic groups other than Caucasians, and in those with genetic enzyme variations.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Only two studies contributed pharmacodynamics data in this submission. Table 7 shows the studies relating to each pharmacodynamic topic.

Table 7. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on pERK inhibition	BRF112680
	Effect on FDG-PET uptake	BRF112680
Secondary Pharmacology	-	
Gender other‡ genetic and Age-Related Differences in PD Response	Effect of gender	-
	Effect of age	-
PD Interactions	Midazolam	BRF112680
Population PD and PK-PD analyses	Healthy subjects	-
	Target population§	Exposure response analysis

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.
‡ And adolescents if applicable.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

5.2.1. Mechanism of action

As was reported by the Sponsor in the Clinical overview:

In vitro studies were reported to show that dabrafenib is a potent and relatively selective inhibitor of the RAF family of kinases including BRAF V600 mutant forms. The mode of action is consistent with ATP competitive inhibition of the RAS/RAF/MEK/ERK (MAP kinase or MAPK) pathway which is involved in normal cellular functions as well as in many human cancers, including approximately 60% of melanomas [3]. Mutation of BRAF in melanoma and other tumours leads to a constitutive activation of the MAPK pathway. BRAF phosphorylates MEK1 and MEK 2 on two regulatory serine residues, resulting in stimulation of cellular growth and inhibition of pro-apoptotic signals.

Dabrafenib is a potent and selective RAF kinase inhibitor of human wild type BRAF and CRAF enzymes as well as the mutation positive forms BRAF V600E, BRAF V600K and BRAF V600D. In *in vitro* studies, dabrafenib was reported to demonstrate suppression of a downstream pharmacodynamics biomarker (phosphorylated ERK [pERK]) in tumour cell lines, demonstrate antiproliferative activity against multiple BRAF mutation positive tumour cell lines, and achieve biomarker suppression and tumour regression in BRAF mutation positive xenograft models.

In vitro studies were also reported to show that sustained dabrafenib presence was required for prolonged tumour growth inhibition (i.e. repeat-dose administration). In addition, it was reported that dabrafenib had a negligible effect on non-proliferating normal human cells, suggesting limited potential toxicity on those cells, and tests on bone marrow progenitor growth suggested that neutropenia was unlikely to be observed at concentrations of dabrafenib required to inhibit tumour growth.

The three active metabolites of dabrafenib (hyroxy-dabrafenib, desmethyl-dabrafenib and to a lesser extent carboxy-dabrafenib) have also been reported to be selective RAF kinase inhibitors based on *in vitro* study results.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

5.2.2.1.1. Phosphorylated ERK (pERK) inhibition

In Study BER114680, pERK expression (as an indication of the mitogen-activated protein (MAP) kinase enzymatic pathway) at baseline and during the first 2 weeks of treatment was evaluated in 8 subjects receiving varying doses of dabrafenib. This showed a median decrease of 83.9% (range: 38.8, 93.3%), with 6/8 subjects showing >80% inhibition of the pERK pathway. A dose-related decrease in pERK was predicted with total daily doses <200 mg (100 mg BID) dabrafenib (gelatine capsules), with a plateau occurring beyond total daily doses of 200 mg thereafter. Therefore, administration of 150 mg BID (gelatine capsules) was predicted to provide, on average, near maximum predicted possible inhibition of this target (~80%) based on the Emax model.

Comment: This study used dabrafenib formulated as gelatine capsules, which have lower bioavailability than the proposed HPMC capsules (see Section 4.2.2.2.3). This is unlikely to greatly affect magnitude of the predicted response as this was predicted to be near maximal, but the question arises as to whether a similar effect could be achieved with lower doses of dabrafenib formulated as HPMC capsules.

5.2.2.1.2. FDG-PET uptake

In Study BRF112680 significant decreases in FDG-PET uptake were observed after 15 days of treatment. Individual maximum standard uptake values (SUVmax) were best modelled using an

[3] Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S et al. Mutations of the *BRAF* gene in human cancer. *Nature,* 2002;417:949-54.

inhibitory Emax model expressed as a function of the daily dose administered (n=60 subjects). The median (95% CI) ED50 was 214 mg (168 to 312 mg).

5.2.2.1.3. Clinical activity

In Study BRF112680 the exposure-response analysis in 89 subjects found that in general, the mean tumour size reduction was related to the daily dose administered. Data were best described using an inhibitory Emax model as a function of the average daily dose administered with a median (95% bootstrap CI) ED50 of 801 mg (571 to 1217 mg). The estimated ED50 was greater than the highest daily dose tested of 600 mg, suggesting that the change in tumour size is very close to being dose-linear. The confirmed ORR at a dose of 150mg BID in Part 1 of the study was 44% (95% CI: 19.8, 70.1), and at a dose of 300mg BID was 70% (95% CI: 34.8, 93.3).

Further analysis of clinical activity according to dose was performed in the dose response analysis which is outlined in Section 5.2.4.

5.2.2.2. Secondary pharmacodynamic effects

Comment: Due to dabrafenib being a new drug, much of the data on secondary pharmacodynamic effects are drawn from preclinical animal studies. These are relevant to the clinical setting as they are the only data available in many cases as no clinical study has been performed.

Preclinical studies were reported to show that dabrafenib and its three active metabolites were generally inactive or displayed reduced potency against a variety of protein and lipid kinases and transmembrane receptors, and were therefore unlikely to have any significant off-target pharmacological activity.

The principal nonclinical toxicology findings associated with dabrafenib treatment were reported to include effects on haematopoiesis/lymphoid tissues, epithelium, testes and embryofoetal development which are likely direct consequences of BRAF inhibition or indirect biological effects likely related to alterations in RAF/MEK/ERK pathway signalling and function.

It was reported in non-clinical repeat dose toxicology studies of dabrafenib in dogs and rats that adverse changes in the right atrium and right atrioventricular valve of the heart (hypertrophy) were observed, along with mild to marked degeneration/necrosis of coronary arterial vasculature associated with haemorrhage, inflammation, and areas of neovascularisation. It was reported that the underlying mechanism(s) involved in cardiovascular lesion development with dabrafenib is unknown, although it was postulated that the effects could be a result of dabrafenib-induced reversible heart rate increases, or as a direct result of BRAF inhibition. It is noted that these cardiac effects were not consistently seen in all studies including those of longer duration and higher dose dabrafenib.

Proliferative skin effects including cutaneous squamous cell carcinoma and keratoacanthoma have been observed in patients given dabrafenib and vemurafenib and are consistent with paradoxical mitogen-activated protein kinase (MAPK)-activation in cells with pre-existing RAS mutations. Epithelial hyperplasia of the forestomach of mice and rats and other tissues, including oesophagus, urinary bladder and renal pelvis, has been reported with other RAF inhibitors, and such findings suggest the proliferative effects may not be limited to human skin. Development of proliferative skin and epithelial forestomach lesions in animals is considered to be pharmacologically-mediated as RAF inhibition can enhance cell growth in wildtype BRAF cells via CRAF dimerisation with subsequent paradoxical activation of RAS/RAF/MEK/ERK pathway signalling.

It was reported that the pharmacology of RAF inhibition suggests theoretical risks for immune-related effects. It was reported that although thymic lymphoid depletion was observed in dogs given dabrafenib, the robust white blood cell responses noted in rat and dog toxicology studies suggest low potential for immunotoxicity.

Testicular toxicity was reported to be observed in mice, rats and dogs given dabrafenib without clear evidence of reversibility following recovery periods of up to 4 weeks, and this was deemed likely to be pharmacologically mediated due to BRAF inhibition in spermatogenesis. These observations are thought likely to translate to human risk.

Reported developmental toxicities from combined female fertility, early embryonic and embryo-foetal development studies in rats suggest human risk for female fertility, embryo-foetal toxicity, including teratogenic effects.

Comment: Based on the preclinical and toxicology studies, it is predicted that there may be secondary pharmacodynamic effects of dabrafenib on the cardiovascular system, proliferative skin effects, and testicular, reproductive and developmental toxicity. There is also a theoretical risk of immunotoxicity.

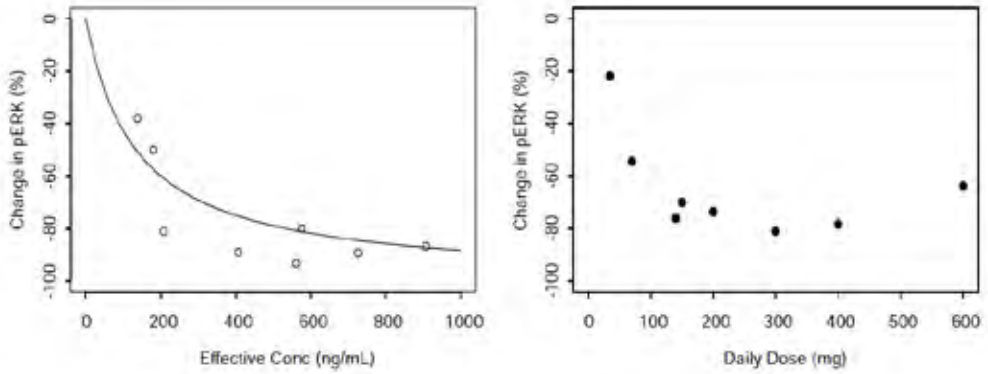
5.2.3. Time course of pharmacodynamic effects

No specific information was provided on the time course of PD effects.

5.2.4. Relationship between drug concentration and pharmacodynamic effects

In Study BRF112680 the relationship between systemic exposure and %pERK inhibition was characterised using a maximum response (Emax) model with 100% maximum inhibition and an IC50 of 134 ng/mL (95% CI: 92.7, 155) on the basis of parent and active metabolite concentrations. The percent change in pERK was predicted by total daily dose on the basis of the mean pre-dose concentrations (Cτ) observed on Day 15, as shown in Figure 1 below. Based on this analysis, a dose-related decrease in pERK was predicted with daily doses <200mg (100mg BID) with response reaching a plateau thereafter due to the plateau in Ctrough exposure.

Figure 1. Observed and predicted individual pERK inhibition (%change from baseline) versus effective concentrations (left panel) and predicted pERK inhibition (% change from baseline) (right panel) based on mean exposure versus daily dose



Data Source: Attachment 8, Figure 1
Left Panel: Symbols indicate individual observed pERK %change from baseline and the line represents predicted response.
Right Panel: Symbols represent predicted responses based on the final model and observed mean Day 15 pre-dose concentrations of GSK2118436, GSK2285403, and GSK2167542.

In this same study (BRF112680), an exposure-response relationship was also observed with FDG-PET as a function of daily dose, with a median (95% bootstrap CI) ED50 of 214 mg (168, 312) dabrafenib. In terms of adverse events, in the first 9 weeks of treatment (prior to dose escalation), the incidence of Grade 3 or 4 AEs was higher in the 100 mg TID, 150 mg BID, 200 mg BID, and 300 mg BID dose cohorts than the lower dose cohorts, the most common being SCC. The AE of pyrexia also appeared to be dose-related. In this study, a MTD was not reached at 300 mg BID, and dose escalation was stopped.

Comment: This Study BRF112680 was the dose finding study used to determine the recommended dose of dabrafenib. It is to be expected that with increasing PD effect with increasing dose, both beneficial and adverse effects would increase. It is accepted that the MTD was not reached in this study.

A PK/PD exposure response analysis was performed based on data from Studies BRF112680 (FTIH), BRF113710 (BREAK-2), and BRF113683 (BREAK-3). It was found that at doses of dabrafenib 150mg BID (HPMC capsules) in the BREAK-3 study, progression free survival (PFS) was similar in subjects whose exposure was above or below the median exposure (Cavg) of 374 ng/mL, and this was likely because the response is at the top of the exposure-response curve.

In this same study, an exposure response relationship was noted using objective response (OR) either at first assessment or confirmed response, with the effect reaching a plateau at an average dabrafenib exposure (Cavg) >300 ng/mL (concentration resulting in >80% of maximum response). Based on the exposure observed with dabrafenib 150mg BID in the Phase II study (gelatine capsules) and the Phase III study (HPMC capsules), 38% and 88% of subjects were predicted to exceed the exposure associated with near maximal response (>300 ng/mL), respectively. These data would suggest that the higher exposure observed with HPMC capsules results in a higher proportion of subjects with efficacious exposure than the same dose administered as gelatine capsules. Subjects with BRAF mutation V600K and high LDH levels had lower response than subjects with BRAF mutation V600E and low LDH levels.

Comment: As noted in the PK/PD analysis evaluation, the impact of dabrafenib exposure on OR was not completely described by the predictive model on visual inspection, and the results should be interpreted with caution.

The exposure response analysis in terms of tumour size (TS) found a significant drug effect on the parameter describing progression, while subjects with higher exposure had longer duration of response than those with lower exposure as development of progression was delayed. Simulations showed that differences in the decrease in tumour size between capsule shells were small (54% of subjects administered HPMC capsules will achieve > 30% reduction in tumour size compared to 51% of subjects given gelatine capsules). Subjects with BRAF V600K mutation had worse outcome with lower response rates and more rapid progression.

Comment: As noted again, the accuracy of the TS model to predict the effect of dabrafenib exposure on TS is likely to be reduced over longer time frames (>100 days), where the model may overestimate the magnitude of the effect of dabrafenib on tumour shrinkage.

Overall, the PK/PD exposure response analysis found that LDH and BRAF V600 mutation type were significant covariates in PFS or OR analyses. Drug effect on tumour size was related to BRAF V600 mutation type, disease state (M1c) and ECOG performance status. In the exploratory adverse event analysis, there was some evidence that higher dabrafenib exposure was associated with higher fraction of subjects with pyrexia. A weaker relationship was noted between exposure and PPE. No exposure response was noted for arthralgia, SCC, and hyperkeratosis.

Comment: It would seem that the recommended dose of dabrafenib 150mg BID in HPMC capsules is supported by the individual PD findings of Study BRF112680 with the dose being over the dose at which pERK inhibition was found to plateau (100mg BID). In addition, the findings of the PK/PD dose response analysis found no significant difference in PFS for the majority of subjects who received dabrafenib 150mg BID HPMC capsules, indicating adequate exposure at this dose range, and 88% of subjects given this dose exceeded the exposure (Cavg >300 ng/mL) associated with near maximal objective response.

5.2.5. Genetic-, gender- and age-related differences in pharmacodynamic response

No information was provided in the submission.

5.2.6. Pharmacodynamic interactions

It was reported that mostly synergistic effects have been observed when dabrafenib was combined with other inhibitors in the MAP kinase pathway such as trametinib (MEK inhibitor) or a PI3K/mTOR inhibitor in BRAF mutant melanoma cell lines in vitro. Similar positive results were also reported to be observed when dabrafenib was combined with trametinib and the angiogenesis inhibitor pazopanib in human tumour xenograft models. Clinical trials of such combination therapies are ongoing.

In a 4 week combination toxicity study in dogs with dabrafenib and trametinib, a MEK1/MEK2 kinase inhibitor, it was reported that no proliferative or hyperkeratotic skin lesions were observed, providing supportive evidence of this likely mechanism (paradoxical mitogen-activated protein kinase (MAPK)-activation in cells with pre-existing RAS mutations) as trametinib would block the downstream signalling of the activated RAF pathway.

Comment: There is a potential synergistic effect of dabrafenib in combination with the MEK inhibitor trametinib, and this combination is the subject of an ongoing study for which the results are not yet available.

5.3. Evaluator's overall conclusions on pharmacodynamics

Only a small amount of PD data was provided with this submission. This could be considered acceptable, as for this indication, it is arguably the clinical efficacy which is of greater clinical relevance than quantification of PD effects.

In Study BRF112680 dabrafenib was shown to inhibit the MAP kinase pathway, measured as dose-related decreases in pERK expression, of the order of 83.9%. Significant decreases in FDG-PET uptake were also observed, with a median (95% CI) ED50 of 214 mg (168 to 312 mg). The mean tumour size reduction was found to be generally related to the daily dose administered, and the estimated ED50 of 801 mg (95% CI: 571 to 1217 mg) was greater than the highest daily dose tested of 600 mg, suggesting that the change in tumour size is very close to being dose-linear. Adverse events (grade 3 and 4) observed at higher dosage ranges included SCC and pyrexia, however the MTD was not reached.

Secondary PD effects taken from preclinical studies anticipated effects on the cardiovascular system, proliferative skin effects, and testicular, reproductive and developmental toxicity. There is also a theoretical risk of immunotoxicity. These potential effects require ongoing monitoring in terms of adverse events. See Sections 8.4.1 and 8.5.5 for further discussion of potential cardiovascular effects and ECG changes including QT prolongation.

The PK/PD exposure response analysis found that at doses of dabrafenib 150mg BID (HPMC capsules), PFS was similar in subjects whose exposure was above or below the median exposure (Cavg) of 374 ng/mL, and this was likely because the response is at the top of the exposure-response curve. An exposure response relationship was noted using objective response (OR) either at first assessment or confirmed response, with the effect reaching a plateau at an average dabrafenib exposure (Cavg) >300 ng/mL, although the model did not precisely fit the observed data. It is noted that the median exposure at the recommended dose is above this level. The exposure response analysis in terms of tumour size (TS) found a significant drug effect on the parameter describing progression, while subjects with higher exposure had longer duration of response than those with lower exposure as development of progression was delayed. In the exploratory adverse event analysis, there was some evidence that higher dabrafenib exposure was associated with higher fraction of subjects with pyrexia and PPE.

6. Dosage selection for the pivotal studies

The dose of dabrafenib selected for use in the three main clinical efficacy and safety studies (BREAK-3, BREAK-2 and BREAK-MB) was 150mg BID. This dose was chosen based on results from the Phase 1 dose-escalation Study BRF112680, where daily doses ranging from 12 to 600 mg were examined.

The dose of 150 mg BID was selected based on 1) the effect of dabrafenib on molecular biomarker targets (e.g., tumour pERK inhibition), 2) FDG metabolic uptake (measured by Day 15 FDG-PET), 3) disease assessment, which was measured by response per Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1 criteria at first evaluation (i.e., weeks 8-9), and 4) overall safety profile. Increasing the dosage from 150mg BID to 200mg BID was not shown to increase the exposure, result in increased inhibition of pERK, or increase the clinical activity in terms of response rate. The safety profile was consistent with that of dosages of 300mg dabrafenib BID, although there were lower numbers of SAEs compared to the 300mg BID dose. A maximum tolerated dose of dabrafenib was not identified in this study.

Comment: Based on the results of Study BRF112680, the selected recommended dose of 150mg BID dabrafenib could be considered the minimum effective dose based on PK, PD, efficacy and safety parameters. It is noted that in this study, the small number of subjects dosed at 300mg BID dabrafenib were found to have a greater clinical response, however the dose of 150mg BID was selected due to the timeliness of the availability of the different cohort results, rather than for any specific PK, PD or safety reasons. Therefore, the potentially increased clinical activity observed at this higher 300mg BID dosage level of dabrafenib may warrant further investigation as a treatment option to improve outcomes, however the effect on the safety profile would also need to be determined.

It is also noted that in the dose-finding Study BRF112680, dabrafenib was formulated in gelatine capsules, which in Study BRF113468 were found to have a lower bioavailability than the proposed HPMC formulation (see Section 4.2.2.2.3). The recommended dose of dabrafenib was not altered with the change in formulation (150mg BID), therefore greater efficacy and safety issues may occur at the proposed dosage and formulation than were observed in the studies using gelatine capsules, which should be considered in the analysis. However, no studies systematically investigated differences in pharmacokinetics, efficacy and safety of the two formulations at the same dosage.

Therefore, the selection of the recommended dosage of dabrafenib 150mg BID in HPMC capsules is not based on ideal pharmacokinetic data, being based on a dose finding study using gelatine capsules which has different bioavailability, and the relative bioavailability of the two formulations has not been directly quantified. However, given the higher bioavailability of dabrafenib as HPMC capsules, and the greater efficacy observed at dosages of 300mg BID using gelatine capsules in the dose finding study and tolerable safety profile with a MTD not reached, selection of the recommended dose could be accepted but there is a need to closely monitor for adverse effects.

7. Clinical efficacy

7.1. Treatment of patients with BRAF V600 mutation positive unresectable or metastatic (Stage IV) melanoma

7.1.1. Pivotal efficacy studies

7.1.1.1. Study BRF113683 (BREAK-3)

7.1.1.1.1. Study design, objectives, locations and dates

Study BREAK-3 was a multi-centre, two-arm, open-label, randomised, active-comparator, Phase III study. It aimed to assess the efficacy of oral dabrafenib compared to intravenous dacarbazine (DTIC) standard of care therapy in subjects with BRAF V600E mutation positive, treatment naive, advanced (unresectable Stage III) or metastatic (Stage IV) melanoma. The safety and tolerability of dabrafenib compared to DTIC would also be assessed.

This study was conducted at 70 centres in 12 countries: Australia (4), Canada (5), France (8), Germany (15), Hungary (2), Ireland (2), Italy (7), Netherlands (1), Poland (4), Russian Federation (5), Spain (9), and the US (9).

Comment: It is noted that the majority of the sites are located in the northern hemisphere, with only 4 centres located in Australia enrolling 16 of the 250 subjects. This may impact on the generalisability of the results to the Australian context, where differences have been shown in the types of V600 mutations that occur in melanoma compared with other regions[4].

This study was initiated on 02 February 2011. The efficacy, safety, health-related quality of life (HRQOL), pharmacokinetic (PK), and BRAF assay validation results presented in the CSR were based on data collected up to the data cut-off date of 19 December 2011, and are the final planned analysis of the primary endpoint, progression-free survival (PFS). Results pertaining to analyses of overall survival (OS), biomarkers and pharmacogenetics (PGx) are planned to be reported at the end of the study, once at least 70% of subjects have died or otherwise been lost to follow-up.

There were four global amendments made to the original study protocol dated 17 August 2010. Of these, the only one with a major impact on the efficacy analysis was the addition of best ORR as a secondary efficacy endpoint on 23 March 2011.

7.1.1.1.2. Inclusion and exclusion criteria

The main inclusion criteria for recruitment were:

- Histologically confirmed advanced (unresectable Stage III) or metastatic (Stage IV) BRAF V600E mutation positive melanoma as determined by central laboratory testing (using an investigational use only (IUO) assay under development for regulatory approval).
- Treatment naïve for advanced/metastatic disease, with the exception of IL-2, surgery, and radiotherapy, which were allowed
- Measurable disease according to RECIST Version 1.1
- Age ≥18 years of age
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1
- Adequate organ function

[4] Long GV, Menzies AM, Nagrial AM, et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. *J Clin Oncol*. 2011;29: 1239-46.

The main exclusion criteria were:

- Ocular or primary mucosal melanoma
- Currently receiving anti-cancer therapy, or use of any investigational anti-cancer or other drug within 28 days of receipt of first dose of dabrafenib
- Major surgery, radiotherapy, or immunotherapy within last 4 weeks
- History of other malignancy
- History of human immunodeficiency virus infection or glucose-6-phosphate dehydrogenase deficiency
- Evidence of active central nervous system (CNS) disease or cardiac metastases
- Cardiac abnormalities

A full list of inclusion and exclusion criteria was provided in the CSR.

Comment: It is noted that patients with brain metastases were excluded from this pivotal study, even though this patient group comprises a large proportion of the proposed target population (it is reported that between 50-75% of patients who die from metastatic (Stage IV) melanoma have been found to have CNS involvement[5]). Although this population group is addressed in a separate study (BRF113929, BREAK-MB, see Section 7.1.2.2), their omission from this study limits the generalisability of the results to this subgroup.

7.1.1.1.3. Study treatments

Subjects were randomised to receive oral dabrafenib 150 mg BID (HPMC capsules) or intravenous DTIC 1000 mg/m^2 every 3 weeks. 3:1 randomisation of dabrafenib to DTIC was implemented to mitigate potential concerns around randomisation to a minimally effective, standard of care such as DTIC in light of emerging clinical data with BRAF inhibitors. Randomisation was stratified for disease stage at baseline (III+IVM1a+IVM1b vs. IVM1c).

Dabrafenib was dosed with 200mL of water, twice a day, at 12-hour intervals and at similar times every day. Dabrafenib was administered under fasting conditions, either one hour before or 2 hours after a meal.

Comment: The dose, formulation and method of administration of dabrafenib used in this study (BREAK-3) are consistent with that proposed for registration in this application.

Dose reductions for dabrafenib and DTIC were permitted according to the study protocol. In addition to the therapies listed under the exclusion criteria, strong inhibitors or inducers of CYP3A4 or CYP2C8, p-glycoprotein (Pgp) or Bcrp transporter were prohibited because they could alter dabrafenib concentrations.

Subjects continued on randomised treatment until disease progression, death, the occurrence of an unacceptable AE, or withdrawal from the study. However, if at disease progression the investigator determined that the subject was still clinically benefitting from dabrafenib, treatment was permitted to continue. Subjects who progressed on chemotherapy were offered therapy with dabrafenib following independently confirmed radiographic progression and were subsequently followed for efficacy and safety including overall survival. 28/63 subjects (44%) randomised to DTIC crossed over to dabrafenib following independently confirmed disease progression.

[5] McWilliams RR, Rao RD, Buckner JC, Link MJ, Markovic S, Brown PD. Melanoma induced brain metastases. *Expert Rev Anticancer Ther* 2008;8:743-55

The BREAK-3 Clinical Study Report (CSR) stated that at the time of study initiation, DTIC, approved for metastatic melanoma and widely used in clinical practice, was considered standard-of-care in unresectable melanoma and confirmed as an acceptable comparator during EU Committee for Medicinal Products for Human Use (CHMP) Scientific Advice. Vemurafenib had not received regulatory approval at the time of initiation of the study or throughout enrolment and so could not be considered as a comparator.

Comment: It is noted that since the initiation of the BREAK-3 study, the BRAF inhibitor vemurafenib has been approved for use in the treatment of advanced or metastatic melanoma in Australia as of May 2012, and has been adopted as best practice treatment for this indication in preference to DTIC according to the National Comprehensive Cancer Network (NCCN) Guidelines (Version 1.2013). Therefore, some assessment of the efficacy and safety of dabrafenib compared to vemurafenib also needs to be made despite no direct head-to-head studies. Comment on this is made in the overall conclusions on efficacy and safety (Sections 7.1.4 and 8.9). In addition, the monoclonal antibody ipilimumab was also approved as a second line therapy for metastatic melanoma in June 2012, and is discussed in the relevant efficacy and safety conclusion sections.

7.1.1.1.4. Efficacy variables and outcomes

The main efficacy variables in Study BRF113683 (BREAK-3) were:

- Progression free survival (PFS) – the interval of time between the date of randomisation and the earlier of either date of disease progression or the date of death due to any cause. Disease progression was based on radiographic or photographic evidence, and assessments made by the investigator according to RECIST 1.1. An independent radiology review (IR), blinded to treatment assignment, was also performed for comparison purposes.
- Overall survival (OS) – the interval of time between the date of randomisation and the date of death due to any cause.
- Overall response rate (ORR) – the percentage of subjects achieving either a complete response (CR) or partial response (PR) according to RECIST 1.1.
- Duration of response – for subjects in the ITT population with a CR or PR, the time from first documented evidence of PR or CR until the first documented sign of disease progression or death due to any cause.
- Health-related quality of life (HRQoL) – this was measured using both the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) and the EuroQol 5D (EQ-5D) questionnaires (both validated).

At baseline, a CT scan of the chest/abdomen/pelvis or MRI of the abdomen/pelvis, MRI of the brain, melanoma skin lesion photography, and clinical disease assessment for palpable lesions was performed. Post-baseline response evaluations were made at Weeks 6, 12, 21, 30, 39, 48, and then every 12 weeks thereafter, according to the schedule of assessments.

The primary efficacy outcome was to evaluate the clinical efficacy of dabrafenib compared to DTIC with respect to PFS, as assessed by the investigator, in subjects with advanced (unresectable Stage III) or metastatic (Stage IV) BRAF V600E mutation positive melanoma.

The selection of PFS in preference to OS as the primary endpoint was justified in the CSR:

> 'The emerging data with BRAF inhibitors effectively precluded the ability to enrol a trial without allowing crossover. Consequently the BREAK-3 trial was designed to evaluate the efficacy of dabrafenib over DTIC while allowing access to dabrafenib upon documented progression to subjects who were randomised to DTIC. Because a large proportion of DTIC subjects were expected to cross over upon progression, the historic

"gold standard" of overall survival (OS) was expected to be confounded. As a result, PFS was chosen as the primary endpoint as it would provide a more direct evaluation of randomised treatment effect.'

Moreover, the Sponsor suggested that PFS had been shown to be a satisfactory surrogate endpoint for OS in other clinical trials [6].

Comment: The justification for using PFS over OS as the primary endpoint is reasonable, and PFS is an acceptable surrogate endpoint for OS in this case. In addition, the use of PFS is considered an acceptable endpoint in the TGA-adopted EMA 'Guideline on the evaluation of anticancer medicinal products in man', as long as OS is reported as a secondary endpoint. In line with the EMA recommendation, independent review has been undertaken in the study.

Important secondary efficacy outcomes included:

- To compare OS between treatment groups.
- To compare best ORR between treatment groups.
- To assess duration of response in subjects receiving dabrafenib for those who experienced a response.
- To assess the best ORR and PFS of subjects in the DTIC treatment group after initial progression and subsequent cross over to dabrafenib.
- To evaluate and compare treatment groups with respect to HRQoL status and symptoms.

Comment: In line with the TGA-adopted EMA guideline, secondary endpoints of OS, ORR and rate of tumour stabilisation (duration of response) have been reported.

7.1.1.1.5. Randomisation and blinding methods

Subjects were centrally randomised (stratified by disease stage) to treatment (3:1 to receive either dabrafenib or DTIC) using a randomisation schedule generated by the GSK Oncology Biometrics Department.

This was an open-label study and treatment was not blinded, however independent radiology review of PFS, blinded to treatment assignment, was performed for comparison purposes.

Comment: It is accepted that due to the different methods of administration, blinding of treatment was not possible in this study. It is appropriate that independent radiological review of PFS occurred, for which there was reduced chance of measurement bias.

7.1.1.1.6. Analysis populations

The intention-to-treat (ITT) population was used to perform the main efficacy analysis, which included all randomised subjects regardless of whether or not treatment was administered. This population was based on the treatment to which the subject was randomised.

Comment: It is agreed that the ITT population is the most appropriate population on which to base the efficacy analysis.

The Safety Population included all randomised subjects who received at least one dose of study drug, and was based on the actual treatment received, if this differed from that to which the subject was randomised.

[6] Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *New Engl J Med.* 2011;364(26):2507-2516.

The Crossover Treatment Population (referred to as Crossover Population) included the subset of subjects who were randomised to the DTIC arm, and who elected at the point of disease progression to receive, and were administered at least one dose of dabrafenib.

7.1.1.1.7. Sample size

Sample size was calculated to show a 200% improvement in median PFS (HR 0.33) between the dabrafenib and DTIC treatment arms. The required number of PFS events to achieve statistical power of 99.7% of rejecting the null hypothesis (H0: $\lambda \geq 1$, where λ is the ratio of the instantaneous hazard of progression or death for BRAF relative to DTIC) if the alternative hypothesis (HA: $\lambda < 1$) is true was 102. Based on a 3:1 (dabrafenib:DTIC) randomisation scheme, a total of 200 enrolled subjects were planned to observe 102 PFS events with the maximum study duration estimated at approximately 12 months.

These hypotheses were to be tested using a one-sided test for superiority with α=0.02. Two-sided confidence intervals with α=0.05 were used in the primary analysis. SAS software (v 9.1.3) was used to perform all data analyses and generate tables, listings, and figures.

The CSR reported that due to unexpectedly rapid recruitment and the large group of subjects from several late-enrolling countries close to the end of recruitment, BREAK-3 enrolled 250 total subjects rather than planned 200.

Comment: The pre-specified treatment effect identified (200% improvement in median PFS) would seem clinically relevant, in light of the traditionally poor prognosis of advanced melanoma, and the relative ineffectiveness of cytotoxic treatments.

7.1.1.1.8. Statistical methods

As reported in the CSR, the primary endpoint of 'PFS was evaluated using the ITT population, and summarised using Kaplan-Meier estimates. Comparisons between treatment arms were made using a stratified log-rank test, stratifying for disease stage at screening (unresectable III+IVM1a+IVM1b vs. IVM1c). The Pike estimator[7] of the treatment HR was provided, together with a two-sided 95% confidence interval (CI). Median and first and third quartile times to PFS were presented, along with approximate two-sided 95% CI, if there were a sufficient number of progressions or deaths. All analyses of PFS were repeated using progression dates from the independent review of PFS.'

Comment: The choice of statistical tests, stratification parameters, and choice of confidence interval for analysis of the primary outcome of PFS would seem reasonable.

With respect to statistical methods used for important secondary endpoints:

- Overall survival included all deaths. For subjects who did not die, OS was censored at the date of last contact. Overall survival was analysed using the ITT population and methods similar to those used in the analysis of PFS.
- The ORR was calculated for the randomised arms using the ITT population, using both the investigator and the independent review assessments of response. Response rates were compared between randomised treatment arms using a Fisher's exact test. An exact 95% CI for the difference in response rates between randomised treatment arms were calculated.
- Duration of response was summarised and listed for the ITT Population using both investigator- and IR-assessed duration of response. If the sample size was sufficient, the median duration of response was calculated from Kaplan-Meier estimates.

Progression-free survival, OS and response were analysed when a minimum of the required number of PFS events (102) had accrued and the study was fully enrolled. A total of 118 PFS

[7] Berry, G., Kitchin, R. M., Mock, P. A. A comparison of Two Simple Hazard Ratio Estimators Based on Logrank Test. *Stat Med*. 1991; 749-55.

events had accrued at the time of data cut-off. The final analysis of OS will be conducted when 70% of subjects have died.

7.1.1.1.9. Participant flow

A total of 733 subjects were screened for enrolment in order to randomise 250 subjects with BRAF V600E mutation positive melanoma into the study. 187 subjects were randomised to receive dabrafenib, with 63 randomised to receive DTIC.

At the time of the clinical data cut-off, 57% of subjects randomised to dabrafenib were still receiving their randomised study treatment, compared to 27% of subjects randomised to DTIC. Twenty-eight subjects randomised to DTIC received dabrafenib in the crossover phase; 21 subjects (75%) were continuing study treatment.

7.1.1.1.10. Major protocol violations/deviations

Deviations to the inclusion and exclusion criteria were identified in 8 subjects (4%) randomised to dabrafenib and 2 subjects (3%) randomised to DTIC. No eligibility waivers were granted for the study, however the incidence of eligibility deviations was assessed in the CSR to be low and unlikely to have a result on study outcomes.

Comment: This assessment is reasonable.

7.1.1.1.11. Baseline data

Subject demographics based on age, race, sex and ethnicity were well balanced between the randomised treatment groups. The mean age was 51.6-53.5 years, and approximately 40% were female. 100% of subjects were classified as white racially.

Comment: The homogeneity of racial groups (only white) may have implications for the use of dabrafenib amongst other racial groups, where the same level of efficacy and safety may not be assured. As discussed earlier (Section 4.2.3.7), there may also be impacts on the PK of dabrafenib across different ethnic groups.

All subjects were diagnosed with Stage III or IV melanoma, with approximately two-thirds having M1c which is indicative of a poorer prognosis.

Comment: It is again noted that although the majority of subjects had metastatic disease, the exclusion of patients with brain metastases excluded a large proportion of the intended target group from this trial.

Approximately half of the subjects had tumours in at least 3 organs in both the treatment arms in the randomised treatment groups. The most common location of disease in both randomised arms were lymph nodes, lung, liver and subcutaneous tissue. Subjects in the dabrafenib arm had a greater proportion of subjects with liver and subcutaneous tissue metastases.

Most subjects in both treatment arms received some type of prior anti-cancer therapy including surgery (96% in the dabrafenib group and 97% in DTIC), immunotherapy (28% and 24%), radiotherapy (20% and 16%) and other biologic, or hormonal therapies. In terms of specific anti-cancer therapy, interferon was the most common which was well balanced between treatment groups (26% in the dabrafenib group and 25% in DTIC). The majority of the prior anti-cancer therapies were adjuvant therapies. As of the data cut-off, 23% of the DTIC arm and 15% of the dabrafenib arm have received follow-up anti-cancer therapy other than dabrafenib as post-treatment anti-cancer therapy.

Comment: As the use of prior anti-cancer therapies was similar between the two treatment arms, this is unlikely to significantly influence the results in favour on one particular treatment.

7.1.1.1.12. Results for the primary efficacy outcome

The key efficacy data for Study BRF113683 (BREAK-3) is summarised below in Table 8.

Table 8. Key efficacy data from the Pivotal Study BREAK-3 (ITT population)

Endpoints/ Assessment	Dabrafenib N=187	DTIC N=63
Progression-free survival		
INV-assessed, median, months (95% CI)	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)
HR (95% CI)	0.30 (0.18, 0.51) p<0.0001	
IRC-assessed, median, months (95% CI)	6.7 (5.0, 6.9)	2.9 (1.7, 4.9)
HR (95% CI)	0.35 (0.20, 0.61)	
Overall survival		
% at 6 months[a] (95% CI)	87 (79.2, 91.9)	79 (59.7, 89.5)
HR (95% CI)	0.61 (0.25, 1.48)	
Overall response[b]		
INV-assessed[c], % (95% CI)	53 (45.5, 60.3)	19 (10.2, 30.9)
IRC-assessed[c], % (95% CI)	50 (42.4, 57.1)	6 (1.8, 15.5)
Overall response duration		
INV-assessed[c]	N=99	N=12
Median, months (95% CI)	5.6 (4.8, NR)	NR (5.0, NR)
IRC-assessed[c]	N=93	N=4
Median, months (95% CI)	5.5 (5.0, 6.7)	NR (NR, NR)

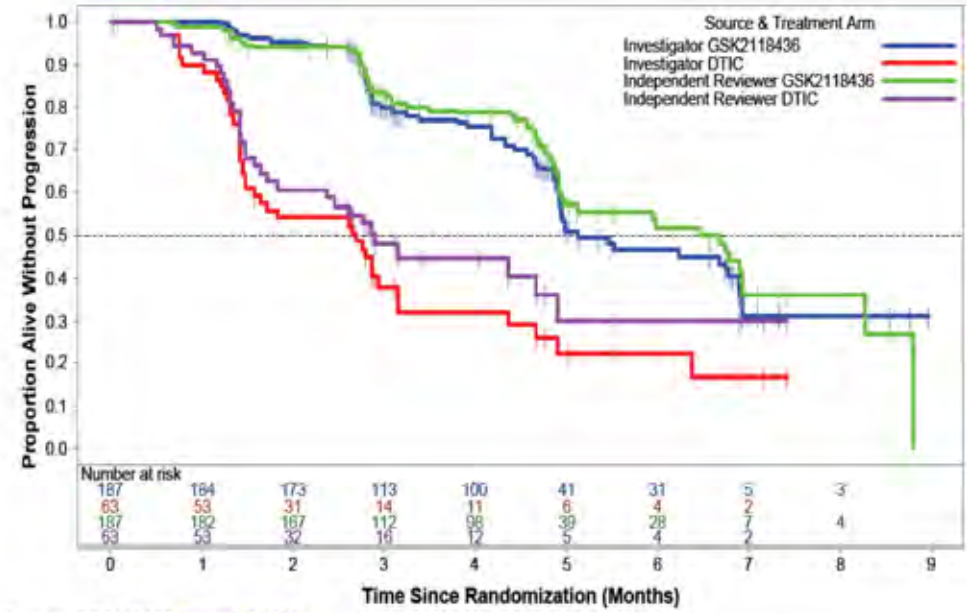
Source: BRF113683 CSR Section 6.2.1 and BRF113683 Table 15, Table 16, Table 17, Table 18 and Table 19; BRF113683 Table 7.4003 and Table 7.4005

Abbreviations: CI: confidence interval; DTIC: dacarbazine; HR: hazard ratio; INV: investigator-assessed; IRC: independent review committee; NR-not reached

a. Estimated from Kaplan-Meier estimates at 6 months; overall survival data are not yet mature and median overall survival has not been reached for either arm.
b. Defined as complete response+partial response.
c. Confirmed response.

In terms of the primary efficacy outcome, the median investigator-assessed PFS for subjects randomised to dabrafenib was 5.1 months (95% CI: 4.9, 6.9) compared to 2.7 months for those randomised to DTIC (95% CI: 1.5, 3.2). This equated to an adjusted hazard ratio of 0.30 (95% CI: 0.18, 0.51; p<0.0001). These results were supported by the independent review results, for which the PFS for subjects randomised to dabrafenib was 6.7 months (95% CI: 5.0, 6.9) and 2.9 months for those randomised to DTIC (95% CI: 1.7, 4.9), with an adjusted hazard ratio of 0.35 (95% CI: 0.20, 0.61). The Kaplan-Meier estimates of PFS by investigator and independent review are shown below in Figure 2. The CSR explained the difference in the independent review and the investigator median PFS estimates as being attributed to variation in early censoring of dabrafenib subjects.

Figure 2. Kaplan-Meier progression-free survival curves (investigator- and independent review-assessed) (ITT population) in Study BRF113683



Source: BRF113683 Figure 17.1010
Abbreviations: DTIC: dacarbazine; GSK2118436: dabrafenib

Comment: These results reveal a statistically significant benefit in median investigator-assessed PFS with dabrafenib compared to DTIC which is supported by independent review. The calculated HR of 0.3 is consistent with the stated hypothesis of a 200% improvement in median PFS with dabrafenib, which was deemed clinically significant. Therefore, according the pre-specified criteria, the results indicate superior efficacy of dabrafenib compared to DTIC in the study population.

It is noted in Figure 2 that the survival advantage of dabrafenib over DTIC appears to decrease over time, however, the low numbers of subjects at latter time points precludes accurate interpretation.

Subgroup analysis of PFS by number of metastatic disease sites, ECOG performance status, visceral disease, baseline LDH, age, sex and disease stage was consistent with the primary analysis. Subgroup analysis by disease stage (separated into either III, IVM1a and IVM1b, or IVM1c) found that subjects with disease Stage III, Stage IV M1a or Stage IV M1b at baseline experienced at hazard ratio of 0.26 (95% CI: 0.10, 0.68) and subjects with disease stage IV M1c at baseline had a hazard ratio of 0.32 (95% CI: 0.17, 0.60). Data for separation into Stage III versus other was not provided, possibly due to low numbers of subjects.

Similarly, sensitivity analysis which involved inclusion of symptomatic progression and subjects who had an extended period of loss to follow-up in PFS events did not alter the results. The Cox proportional hazards model identified baseline LDH and age as statistically significant prognostic factors, although PFS HRs still remained significant within all LDH and age groups.

7.1.1.1.13. Results for other efficacy outcomes

Overall survival: The OS data were not yet mature at the time of data cut-off, with median OS not reached in either arm. The interim OS analysis showed a trend towards improved survival for dabrafenib over treatment with DTIC, with a hazard ratio of 0.61 (95% CI: 0.25, 1.48). The Kaplan-Meier estimates of OS at 6 months were 87% (95% CI: 79.2, 91.9) in the dabrafenib arm and 79% (95% CI: 59.7, 89.5) in the DTIC arm (which included subjects who crossed over to dabrafenib on disease progression).

Overall response rate: Both unconfirmed and confirmed response rates were reported for investigator- and independent radiologist-assessed ORR. The investigator-assessed best confirmed ORR was 99/187 subjects (53%, 95% CI: 45.5-60.3%) in the dabrafenib arm compared to 12/63 subjects (19%, 95% CI: 10.2-30.9%) in the DTIC arm. The unconfirmed ORRs were higher than the confirmed rates. Independent radiologist-assessed response rates for the dabrafenib arm were consistent with investigator-assessed response rates (50% and 53% respectively); however, the independently-assessed response rates for the DTIC arm were lower than the investigator-assessed response rate (6% compared to 19% respectively).

Duration of response: Subjects treated with dabrafenib who experienced a confirmed response had an investigator-assessed duration of response of 5.6 months (95% CI: 4.8, NR). Among subjects treated with DTIC who responded, only 1 (of 12) had progressed, with duration of response of 5 months. The independent assessment of duration of response was similar to the investigator assessment. Subjects treated with dabrafenib who experienced a confirmed response had an independent radiologist-assessed duration of response of 5.5 months (95% CI: 5.0, 6.7 months).

Crossover phase efficacy results: The median time on dabrafenib after crossover was 2.8 months. The median PFS in the crossover phase at the time of data cut-off was 4.1 months. The unconfirmed response rate in the crossover phase was 46% (95% CI: 27.5-66.1%), however the duration of follow up was insufficient to confirm this response. Duration of response was 10.3 weeks or 2.4 months, however this is expected to change with longer follow-up.

Comment: The results of the secondary efficacy outcomes are consistent with that of the primary outcome, PFS, with greater benefit for subjects treated with dabrafenib than with DTIC for all outcomes measured. OS was longer for dabrafenib, despite allowing for crossover upon disease progression in the DTIC arm, which is likely to dilute the degree of benefit. The ORR was found to be significantly greater for subjects treated with dabrafenib compared to subjects treated with DTIC. In subjects who crossed over to dabrafenib from DTIC, PFS was longer and ORR was greater than was seen in the same subjects on previous treatment with DTIC. Therefore, analysis of these secondary endpoints supports the observed benefit of dabrafenib on the primary outcome, PFS.

Health-related quality of life measures:

- EORTCQLQ-C30: Comparable levels of functional dimensions and symptoms-related HRQoL were reported from subjects in both arms at screening. There were no clinically significant differences observed on overall global health status between the two arms for the duration of the study. Functionality scores were generally lower (lower level of functioning) in the DTIC arm than the dabrafenib arm throughout the study, particularly physical, cognitive and emotional functioning. Symptom scores were generally lower than baseline (improved symptoms) during treatment for the dabrafenib arm, and were higher (worse symptoms) than baseline for the DTIC arm.
- EQ-5D: Baseline measurements were similar between the two groups. There was some improvement in subjects' reporting of pain or discomfort or anxiety or depression in both treatment arms during treatment, with subsequent worsening on disease progression.

Comment: The HRQoL results, suggest some quality of life benefits for subjects treated with dabrafenib compared to DTIC in terms of functionality and the presence of symptoms, however the degree of difference is variable at different time-points, different domains, and different measuring techniques. In all cases, functionality and symptoms tended to deteriorate on disease progression, although improvements were seen on crossover to dabrafenib for patients who progressed on DTIC.

7.1.2. Other efficacy studies

7.1.2.1. Study BRF113710 (BREAK-2)

Study BRF113710 (BREAK-2) was a multi-centre, single-arm, Phase II, open-label study. The main purpose was to evaluate the efficacy of dabrafenib (gelatine capsules, 150mg BID) in adult subjects (aged ≥18 years) with BRAF V600E or V600K mutation positive metastatic (Stage IV) melanoma. Key inclusion and exclusion criteria were similar to that of the pivotal study BRF113683 (BREAK-3), apart from the inclusion in this study of not only treatment-naïve subjects, but also those who had received prior treatment in the metastatic setting (i.e., chemotherapy, immunotherapy, prior targeted therapy, etc.) and also subjects with BRAF V600K mutations. Those with CNS metastases or who had undergone treatment with another BRAF or MEK inhibitor were excluded. Of 211 subjects screened for enrolment, 152 had a BRAF V600E or V600K mutation, and 92 of these (76 with BRAF V600E mutation and 16 with V600K) entered into the study. Of those enrolled, the median age was 55.5 years, 53% were male and 99% were White. 74/92 (80%) had received prior chemotherapy (the most common being dacarbazine, interferon, temozolomide, cisplatin, interlukin-2 and ipilimumab) and 98% had received prior surgery. Subjects continued on treatment until disease progression, death, or unacceptable adverse event.

Comment: The formulation of dabrafenib in this study in gelatine capsules is different to that proposed for registration in HPMC capsules. See Section 3.2 for a discussion of the implications of this for interpretation of results.

It is also noted that the number of subjects enrolled in this study with BRAF V600E mutation (76) was lower than the 85 subjects specified in the protocol calculated as the sample size required to test the hypothesis that there is a clinically meaningful response rate (CR or PR ≥ 40%). This was explained by there being a higher than expected screen failure following initial subject registration. It was argued in the CSR that this number still retained adequate study power to demonstrate a clinically meaningful response rate, however this statement was not supported by quantitative estimates, and needs to be considered in the interpretation of results.

The primary objective was to assess ORR, defined as the proportion of subjects with investigator-assessed complete response (CR) or partial response (PR) in subjects with BRAF V600E mutation positive metastatic melanoma treated with dabrafenib. Disease progression and response evaluations were determined according to the definitions established in the RECIST 1.1, with confirmation of CR and PR required. In addition to investigator assessment, scans were independently reviewed. The pre-specified null hypothesis was that the ORR was not clinically meaningful (≤25%), while the alternative hypothesis was a clinically meaningful ORR (≥40%). Relevant secondary objectives included assessment of ORR in subjects with BRAF V600K mutation positive metastatic melanoma, and assessment of PFS, duration of response and OS in BRAF V600E and V600K positive subjects, and to assess safety and population PK parameters.

The main results of Study BRF113710 (BREAK-2) are presented below in Table 9.

Table 9. Key efficacy data from the supportive Study BREAK-2 (All treated subjects)

Endpoints/ Assessment	BRAF V600E (Primary) N=76	BRAF V600K N=16
Overall response		
INV-assessed[a], % (95% CI)	59 (48.2, 70.3)	13 (0, 28.7)
IRC-assessed[a], % (95% CI)	41 (29.7, 51.8)	25 (3.8, 46.2)
Response duration		
INV-assessed	N=45	N=2
Median, months (95% CI)	5.2 (3.9, NR)	5.3 (3.7, 6.8)
IRC-assessed	N=31	N=4
Median, months (95% CI)	6.2 (5.1, NR)	5.0 (3.4, NR)
Progression-free survival		
INV-assessed, median, months (95% CI)	6.3 (4.6, 7.7)	4.5 (2.6, 6.2)
IRC-assessed, median, months (95% CI)	6.1 (4.6, NR)	4.5 (2.6, 6.2)
Overall survival		
Primary analysis at 6 months follow-up, median, months (CI)	9.5 (9.5, NR)	7.9 (5.5, NR)
Updated analyses at 12 months follow-up[b], median, months (CI)	13.1 (10.4, NR)	12.9 (6.9, 17.1)

Source: BRF113710 CSR Table 13, Table 14, Table 15; BRF113710 Table 7.106, Table 7.107, Table 7.108, Table 7.109 Table 7.110, Table 7.112, Table 7.113, Table 7.114, Table 7.115; Table 7.16, Table 7.17, Table 7.18, Table 7.19

Abbreviations: CI: confidence interval; INV: investigator-assessed; IRC: independent review committee; NR-not reached

a. Confirmed response.
b. Updated analyses at 30 April 2012 data cut-off.

For the primary outcome of investigator-assessed ORR in the BRAF V600E population, 45/76 subjects (59%, 95% CI 48.2-70.3%) had a confirmed response, of which 5/76 (7%) were a CR and 40/76 (53%) a PR. 12/76 (16%) had stable disease (SD), while 12/76 (16%) had progressive disease (PD). Subgroup analysis by age and gender did not reveal any significant differences. The response by independent review was lower than that assessed by the investigators, with ORR in the BRAF V600E population being 31/76 subjects (41%, 95% CI 29.7-51.8%).

In terms of secondary outcomes, PFS in the BRAF V600E population was assessed by the investigator as 27.4 weeks (95% CI 19.9-33.4), and by the independent reviewer as 26.7 weeks (95% CI 20.0-NR), although the data was not yet mature. The median duration of response in the V600E subjects was investigator assessed as 22.4 weeks (95% CI 17.1-NR) and independent reviewer assessed as 26.9 weeks (data not yet mature). At the time of data cut-off, the median follow-up time was 6.5 months, and 70% of the BRAF V600E population were still alive, thus OS data was not yet mature, and a median OS estimate could not be determined.

Comment: Although it was reported in the CSR that OS data was not mature, it is noted that OS results were presented in the Clinical summary (see Table 9 above). Summary tables for the 6 month analyses was provided in the appendices of the CSR, however the updated 12 month values were not included in the submission and therefore cannot be verified.

In the BRAF V600K population, 2/16 subjects (13%) had an investigator-assessed confirmed response (both a PR), 7/16 (44%) had SD, and 5/16 (31%) had PD. In contrast to the V600E population, in the V600K population the independent-assessed response was higher than measured by the investigators, with an ORR of 4/16 subjects (25%). PFS in the BRAF V600K population was assessed by the investigators to be 19.7 weeks (95% CI 11.1-27.0), the same as by the independent-reviewer: 19.7 weeks (95% CI 11.1-27.0). Duration of response in the V600K population was hampered by low numbers of responders, but was measured by the investigator at a median 22.9 weeks, and the independent reviewer as 21.7 weeks. OS data for

the V600K population was not mature at the time of data cut-off, and therefore median OS was not reported in the CSR (although provided in the table above – refer to above comment).

Due to the relatively high level of discordance between response assessments by investigators and independent reviewers (34% (26/76) discordance in the BRAF V600E population, and 25% (4/16) in the V600K population), an independent third party adjudicator reviewed both sets of response data for each subject with discordance. The adjudicator's assessment was more consistent with the investigator-assessed response rate in the V600E population, and between the two assessments for the V600K population. It was assessed that there did not appear to be systematic reasons for the discordance or any apparent bias leading to the discordance, but rather the likely reasons were considered to be heterogeneous responses amongst differing lesions (multiple sites of metastases and multiple target lesions) and imaging variability.

Comment: It is accepted that difficulties in assessment of the condition will lead to discordance in response assessment by the different assessors. Keeping this in mind, it is therefore noted that the true response rate of dabrafenib in the V600E population in this study may in fact be lower than that measured by the investigator and recorded as the primary outcome (at 59%), and the ORR as measured by the independent assessor (41%) should also be considered.

Taking the above into account, the results of Study BRF113710 (BREAK-2) are consistent with the results of the pivotal study BRF113683 (BREAK-3). The primary outcome of ORR at 59% (or 41% on IR) is in line with the ORR of 53% seen in the dabrafenib arm of the BREAK-3 study, and is clinically meaningful in line with the pre-specified hypotheses (ORR ≥40%) despite insufficient study enrolment. PFS results are also in line with the 5.1 months seen in the BREAK-3 study, and duration of response at 5.6 months. Therefore, the results of this study support the findings of the pivotal study in a similar (BRAF V600E) population for whom previous treatment is allowed.

The ORR for subjects with BRAF V600K mutations was less than that of the V600E population at 13% (25% IR). It is noted that small numbers preclude accurate interpretation of these results, and the lack of a direct comparator in this Phase II study hinders the analysis. It is noted that this ORR is similar to that of the DTIC arm for V600E subjects in the BREAK-3 study at 19%, although PFS (19.7 weeks for V600K subjects in this study) was longer than the 2.7 months observed for the DTIC group in BREAK-3.

As discussed, one difference in the conduct of this study was the use of gelatine dabrafenib capsules rather than HPMC as used in the BREAK-3 study and proposed for registration. However, as use of gelatine capsules was found to result in reduced bioavailability, the predicted effect would be to reduce the efficacy of treatment, and result in underestimation of efficacy results compared to use of HPMC capsules. It is considered unlikely that the difference in formulation could result in overestimation of the efficacy results.

7.1.2.2. Study BRF113929 (BREAK-MB)

Study BRF113929 (BREAK-MB) was a global, multi-centre, open-label, single-arm, two-cohort, Phase II study designed to prospectively evaluate the activity of dabrafenib (150mg BID, HPMC capsules) in subjects with histologically confirmed (Stage IV) BRAF-mutation-positive (V600E or V600K) melanoma metastatic to the brain. 89 subjects were enrolled into Cohort A (subjects with no prior local therapy for brain metastasis) and 83 into Cohort B (subjects who had failed prior local therapy for brain metastasis). Of the total 172 subjects, 139 had V600E mutation, and 33 had V600K. Concomitant use of corticosteroids (36% in Cohort A and 49% in Cohort B) had to be on a stable or decreasing dose at the time of first dose study treatment. Previous systemic treatments (excluding BRAF and MEK inhibitors) were allowed. Baseline characteristics for all

subjects were a mean age of 52.5 years, 70% male, 100% white and 81% V600E mutation-positive. These characteristics were generally evenly distributed between both cohorts. In keeping with the cohort definitions, subjects in Cohort B had a greater number of intracranial lesions than those in Cohort A, and had received more prior anticancer therapy (including radiotherapy, chemotherapy and immunotherapy).

The primary objective of the study was to assess the overall intracranial response rate (OIRR), defined as the proportion of subjects with confirmed complete intracranial responses or partial intracranial responses assessed by investigators, in V600E mutation-positive subjects. Assessments were made using contrast-enhanced MRI, with independent radiologist review. Disease progression and response evaluations for intracranial disease were determined according to the definitions established in RECIST 1.1, with minor modifications regarding the number (up to 5) and size (≥ 5mm in longest diameter) of target lesions.

The pre-specified null hypothesis was an OIRR ≤ 10%, with the alternative hypothesis the clinically relevant OIRR of ≥30% in subjects with V600E mutations, with a planned sample size of 60 V600E positive subjects per cohort. Secondary endpoints included estimation of the overall ORR (combined extracranial and intracranial response), duration of intracranial and overall response, PFS and OS in V600E mutation-positive subjects, and also estimation of all the same endpoints in subjects with BRAF V600K mutations. Other secondary objectives included characterisation of the safety and tolerability of dabrafenib, and assessment of PK parameters of dabrafenib and its metabolites.

Comment: In general, due to the inclusion of subjects with brain metastases in this study (BREAK-MB), and their specific exclusion in the other two efficacy studies (BREAK-3 and BREAK-2), the patient population in this study is likely to have more advanced disease (due to CNS involvement). This may have implications for the interpretation and generalisability of both efficacy and safety results that require consideration. Also, the high proportion of patients on concomitant dexamethasone (a corticosteroid commonly used in subjects with brain metastases and a cytochrome P450 CYP3A4 substrate) in this study may also impact on the results, since dabrafenib is also metabolised by CYP3A4 (see Section 4.2.2.4.2).

The main results for Study BRF113929 (BREAK-MB) are shown below in Table 10.

Table 10. Key efficacy data from the key Study BREAK-MB (All treated subjects)

	BRAF V600E (Primary)		BRAF V600K	
Endpoints/ Assessment	**Cohort A N=74**	**Cohort B N=65**	**Cohort A N=15**	**Cohort B N=18**
Overall intracranial response rate, % (95% CI)				
INV-assessed[a]	39 (28.0, 51.2)	31 (19.9, 43.4)	7 (0.2, 31.9)	22 (6.4, 47.6)
IRC-assessed[a]	20 (11.8, 31.2)	18 (9.9, 30.0)	0 (0, 21.8)	11 (1.4, 34.7)
Overall intracranial response duration, median, months (95% CI)				
INV-assessed	N=29 4.6 (2.8, NR)	N=20 6.5 (4.6, 6.5)	N=1 2.9	N=4 3.8 (NR, NR)
IRC-assessed	N=15 4.7 (4.5, 6.5)	N=12 4.6 (4.2, 4.6)	NA	N=2 NR
Overall response, % (95% CI)				
INV-assessed[a]	38 (26.8, 49.9)	31 (19.9, 43.4)	0 (0, 21.8)	28 (9.7, 53.5)
IRC-assessed[a]	28 (18.5, 40.1)	23 (13.5, 35.2)	0 (0, 21.8)	11 (1.4, 34.7)
Overall response duration, median, months (95% CI)				
INV-assessed	N=28 5.1 (3.7, NR)	N=20 4.6 (4.6, 6.5)	NA	N=5 3.1 (2.8, NR)
IRC-assessed	N=21 4.6 (4.3, NR)	N=15 4.6 (2.8, NR)	NA	N=2 NR
Progression-free survival, median, months (95% CI)				
INV-assessed	3.7 (3.6, 5.0)	3.8 (3.6, 5.5)	1.9 (0.7, 3.7)	3.6 (1.8, 5.2)
IRC-assessed	3.6 (2.6, 5.2)	3.7 (3.5, 3.8)	1.8 (0.7, 1.9)	3.5 (1.9, 5.6)
Overall survival				
Median, months (95% CI)	7.6 (5.9, NR)	7.2 (5.9, NR)	3.7 (1.6, 5.2)	5.0 (3.5, NR)

Source: BRF113929 CSR Table 11 to Table 12 and Table 20 to Table 21; BRF113929 Table 7.2005, Table 7.2006, Table 7.3005, Table 7.3006, Table 7.6005, Table 7.6006, Table 7.7003, Table 7.7004, Table 7.8013, Table 7.8014, Table 7.8015, Table 7.8016, Table 7.9009, Table 7.9010

Abbreviations: CI: confidence interval; INV: investigator-assessed; IRC: independent review committee; NA: not applicable; NR: not reached

a. Confirmed response.

Cohort A: subjects with no prior local therapy for brain metastasis.

Cohort B: subjects who received prior local therapy for brain metastasis.

For the primary efficacy endpoint in subjects with V600E mutation-positive melanoma, the investigator assessed OIRR (CR+PR) was 29/74 subjects (39%, 95% CI 28.0-51.2) in Cohort A, and 20/65 subjects (31%, 95% CI 19.9-43.4) in Cohort B. SD was seen in 31/74 (42%) in Cohort A and 38/65 (58%) in Cohort B, with PD in 9/74 (12%) in Cohort A and 5/65 (8%) in Cohort B. However with independent reviewer assessment, the results were less favourable, with an OIRR in Cohort A of 15/74 (20%, 95% CI 11.8-31.2) and in Cohort B of 12/65 (18%, 95% CI 9.9-30.0), SD was seen in 25/74 (34%) in Cohort A and 25/65 (38%) in Cohort B, and PD seen in 17/74 (23%) in Cohort A and 15/65 (23%) in Cohort B. Concordance between the OIRR assessment of investigators and independent reviewers was found to be 62%, and a blinded, third-party adjudication was performed on the discordant cases which affirmed the investigator assessment 68% of the time and the independent review assessment 32% of the time. The adjudicated investigator-assessed confirmed OIRR was 35% in Cohort A and 29% in Cohort B, which are more similar to the investigator-assessed results. Reasons given for the discrepancies in assessments were the heterogeneity among target lesions, lesion necrosis or haemorrhage during treatment, variability of image acquisition technique, and borderline response and progression.

Comment: As with the BREAK-2 study, difficulty in making reproducible assessments is acknowledged, however this impacts on the precision of the results and therefore the way in which they are interpreted. In this case, again it should be noted that the true OIRR may be less than that determined by the investigators (39% in Cohort A), and may be closer to that of the independent reviewer (20%). As the pre-specified clinically relevant OIRR was ≥30%, this is important in assessing impact of the result.

Assessment of the clinical relevance of this outcome is also hampered due to the Phase II nature of this trial, and the absence of a comparator arm; specifically local management of brain metastases using techniques such as surgery or stereotactic radiosurgery (SRS) which have shown documented improvements in survival[8]. It is not possible to accurately assess the efficacy of dabrafenib in CNS metastases compared to these currently used techniques.

In terms of secondary endpoints in V600E mutation-positive subjects, the median duration of investigator-assessed intracranial response was 20.1 weeks in Cohort A and 28.1 weeks in Cohort B (20.3 weeks and 20.1 weeks respectively with IR). Investigator-assessed ORR was 38% in Cohort A and 31% in Cohort B (28% and 23% with IR), with SD 42% in Cohort A and 52% in Cohort B (26% and 42% with IR), and PD 15% in Cohort A and 14% in Cohort B (35% and 25% with IR). Median investigator-assessed duration of overall response was 22.1 weeks in Cohort A and 20.1 weeks in Cohort B (20.1 weeks and 20.1 weeks with IR). The investigator-assessed median PFS for subjects with V600E mutation-positive melanoma was 16.1 weeks in Cohort A and 16.6 weeks in Cohort B (15.7 weeks and 16.0 weeks with IR). The median OS in V600E positive subjects was 33.1 weeks in Cohort A and 31.4 weeks in Cohort B.

Comment: Again there appears to be a relatively high degree of discordance in the ORR assessments made by the investigators and independent reviewers, with the latter being lower. It is likely that the same explanations as for the OIRR results apply, as does the subsequent need for caution in the interpretation of the investigator-assessed results which may be higher than the true values.

It is interesting that the results are more favourable for Cohort B than Cohort A in terms of duration of intracranial response and PFS, as the converse may have been expected due to there being more advanced disease at baseline in Cohort B (and a higher intracranial disease burden in terms of number of lesions at baseline despite prior therapy). Thus there may be an additive effect of dabrafenib with the previous local therapies on intracranial lesions. Results for OIRR, ORR and duration of overall response are similar in both cohorts, therefore implying that the intracranial effects of dabrafenib remain effective in the presence of more extensive intracranial disease.

Subgroup analysis of OIRR, ORR and duration of response in V600E positive patients based on whether there had been prior systemic therapy tended to slightly favour those without prior systemic therapy in Cohort A, however there was minimal difference between the two subgroups in Cohort B.

For the secondary endpoints in subjects with V600K mutation-positive melanoma, investigator-assessed OIRR was 1/15 subjects (7%) in Cohort A and 4/18 (22%) in Cohort B (0% and 11% with IR), with SD seen in 4/15 (27%) in Cohort A and 5/18 (28%) in Cohort B (20% and 22% with IR). Intracranial PD occurred in 6/15 (40%) in Cohort A and 6/18 (33%) in Cohort B (53% and 33% with IR). The investigator-assessed ORR in V600K positive subjects was 0% in Cohort A and 28% in Cohort B (0% and 11% with IR), while PD occurred in 27% in Cohort A and 33% in Cohort B (60% and 33% with IR). Median PFS in V600K subjects was investigator-assessed as 8.1 weeks in Cohort A and 15.9 weeks in Cohort B (7.9 and 15.3 weeks with IR). The median OS in V600K positive subjects was 16.3 weeks in Cohort A and 21.9 weeks in Cohort B.

Comment: It can be seen that although small numbers necessitate careful interpretation, the results for all endpoints are generally lower in subjects with V600K mutations compared to those with V600E mutations. Specifically OIRRs are low, in Cohort A (at 7% and 0% on IR) being in keeping with the null hypothesis of no effect (≤10%). In addition, rates of PD were higher, being the best response in 40% of subjects in Cohort A (53% with IR). The one exception is PFS in Cohort B patients

[8] Carlino MS, Fogarty GB, Long GV. Treatment of melanoma brain metastases. *Cancer J* 2012;18:208-12.

which are similar for the V600E and V600K populations (16.6 weeks vs. 15.9 weeks), but low numbers (N=5) preclude accurate interpretation. These results indicate that the effectiveness of dabrafenib in patients with V600K mutation-positive melanoma appears to be substantially less than its effectiveness in V600E positive subjects, and any beneficial claims over conventional management are not definitive.

Again the outcomes have been assessed as higher by the investigator than the independent reviewer, and the same caution in the interpretation of results as discussed previously applies.

7.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

An 'Integrated Summary of Efficacy' was provided in Module 5, which was the same as the 'Summary of Clinical Efficacy' presented in Module 2 (2.7.3). No new information beyond what was provided in the CSRs was included in this summary.

7.2. Evaluator's conclusions on clinical efficacy of dabrafenib for treatment of patients with BRAF V600 mutation positive unresectable or metastatic (Stage IV) melanoma

One pivotal study (BREAK-3), and two supportive studies (BREAK-2 and BREAK-MB) were submitted with this application in support of the proposed indication of use of dabrafenib for treatment of patients with BRAF V600 mutation positive unresectable or metastatic (Stage IV melanoma). Evaluators conclusions based on the data submitted are as follows:

7.2.1. BRAF V600E mutation positive advanced or metastatic melanoma (excluding brain metastases)

For patients with treatment naive V600E positive metastatic melanoma, the BREAK-3 study with 250 subjects (187 randomised to dabrafenib and 63 to DTIC) showed a statistically significant and clinically relevant improvement in the primary endpoint of investigator-assessed PFS compared to DTIC of 5.1 months compared to 2.7 months respectively, equating to an adjusted hazard ratio of 0.30 (95% CI: 0.18-0.51; p<0.0001). This result was supported by independent review, and also by the secondary endpoints of OS (87% at 6 months for dabrafenib compared to 79% for DTIC), ORR (53% for dabrafenib compared to 19% for DTIC), and duration of response (5.6 months for dabrafenib compared to 5 months for DTIC). Quality of Life measures also indicated an advantage for dabrafenib over DTIC. These results were supported by Study BRF113701 (BREAK-2) in patients with previously treated metastatic BRAF V600E melanoma. The primary endpoint showed a favourable investigator-assessed ORR of 59% (41% on independent review), along with a PFS of 6.3 months and duration of response of 5.2 months. Therefore, the results of the BREAK-3 study, supported by the BREAK-2 study, indicate that the efficacy of dabrafenib is clinically superior to DTIC in the treatment of patients with advanced or metastatic (excluding brain metastases) BRAF V600E mutation positive melanoma.

7.2.2. BRAF V600E mutation positive metastatic melanoma to the brain

Patients with brain metastases were excluded from the pivotal BREAK-3 and supportive BREAK-2 study. As the frequency of CNS metastases in those who die from metastatic melanoma has been found to be 50-75%[9], a large proportion of the intended target population has therefore been excluded from this pivotal trial. The BREAK-MB study assessed the effects of dabrafenib in 139 subjects with BRAF V600E mutation positive metastatic melanoma to the

[9] McWilliams RR, Rao RD, Buckner JC, Link MJ, Markovic S, Brown PD. Melanoma induced brain metastases. *Expert Rev Anticancer Ther* 2008;8:743-55

brain, however as a Phase II study, the absence of a comparator limits the interpretation of results.

The primary endpoint in the BREAK-MB study of investigator-assessed OIRR in V600E mutation positive subjects suggested a clinically beneficial effect of either 31 or 39% (depending on the previous use of local treatment), however the results with independent review were less convincing (18 or 20%). The investigator-assessed ORR in this group of patients of 31 or 38% (23 or 28% with IR) was less than in the BREAK-3 and BREAK-2 studies, and this is not unexpected due to patients in the BREAK-MB study having more advanced disease resulting in brain metastases. Similarly, results for median duration of response (20.1 or 22.1 weeks) and PFS (16.1 or 16.6 weeks) were shorter in this study. The median OS was 31.4 or 33.1 weeks.

The absence of a control population in the BREAK-MB study was justified in the CSR due to there being no currently available active systemic therapy for use in melanoma patients with CNS involvement. However, it could be argued that there are currently available local therapies with demonstrated effectiveness such as surgery and stereotactic radiosurgery (SRS) (up to 40 weeks median survival reported[10] , and these would be appropriate comparators in a Phase III trial. No data was presented by the Sponsor comparing the efficacy of dabrafenib with these local therapies. Therefore, pending more definitive evidence, although it would seem efficacious, it cannot be concluded that dabrafenib is superior to currently used local therapies in the management of BRAF V600E positive metastatic melanoma CNS lesions. It is recommended that more information be provided by the Sponsor to specify the proposed use of dabrafenib in the setting of BRAF V600E positive melanoma brain metastases. Specific questions include whether dabrafenib should be used prior to, after, or instead of local management (surgery or SRS) that is deemed appropriate using current criteria. In addition, under what circumstances (e.g. degree of tumour burden) are the different treatments are deemed appropriate? It is noted that this conclusion is not entirely consistent with that of the Sponsor.

7.2.3. BRAF V600K mutation positive metastatic melanoma

Patients with BRAF V600K mutation positive metastatic melanoma were excluded from the pivotal BREAK-3 study, but were assessed in the Phase II BREAK-2 and BREAK-MB studies. Therefore, the results for this subgroup are limited by small numbers and the absence of an active comparator. Assessment of V600K mutation positive subjects was not a primary endpoint in either of the BREAK-2 or BREAK-MB studies.

For 16 subjects in the BREAK-2 study, the ORR for subjects with BRAF V600K metastatic melanoma excluding brain metastases was 13% which is more consistent with that seen in the DTIC arm in the BREAK-3 study. Some improvements in PFS (4.5 months) and duration of response (5.3 months) were observed compared to historical studies.

For 33 subjects in the BREAK-MB study, the investigator-assessed OIRR for patients with V600K positive metastatic melanoma to the brain was 7 or 22% depending on prior local treatment (0 or 11% with IR), while ORR was 0 or 28% (0 or 11% with IR), median PFS was 8.1 or 15.9 weeks (7.9 or 15.3 weeks with IR), and median OS was 16.3 or 21.9 weeks.

The results of both these studies do not meet the pre-defined criteria for clinical significance[11], and in any case with low numbers, lack of an active comparator, and as secondary endpoints, interpretation is limited. Therefore, the opinion of this evaluator is that the submitted evidence for the efficacy of dabrafenib in patients with BRAF V600K mutation positive metastatic melanoma is not convincing, and the clinical significance in this patient population remains undetermined. Particularly with respect to patients with BRAF V600K metastatic melanoma to

[10] Carlino MS, Fogarty GB, Long GV. Treatment of melanoma brain metastases. *Cancer J* 2012;18:208-12.
[11] Sponsor comment: This does not apply to BRF113929 (BREAK-MB). The intracranial and overall response rates were secondary endpoints for the V600K mutation positive subjects for which no pre-defined criteria for clinical significance was defined, either in the protocol or the Reporting and Analysis Plan (RAP).

the brain, there is no evidence of superiority of dabrafenib compared to appropriate local management (surgery of SRS). The claim in the BREAK-MB CSR that treatment with dabrafenib in V600K subjects with metastatic melanoma to the brain is clinically significant based on the PFS and OS being longer than observed with systemic chemotherapy, is debatable in light of the limitations of the evidence.

However, due to the poor prognosis of metastatic melanoma and, until recently, the lack of an effective treatment, there may be a role for treatment of patients with BRAF V600K metastatic melanoma, provided the limitations in the evidence with regards to this patient subgroup are acknowledged and ongoing data is collected for further assessment.

7.2.4. Comparison of dabrafenib with the BRAF inhibitor vemurafenib and the monoclonal antibody ipilimumab

One major limitation of the data submitted in this application was the lack of comparison of dabrafenib with the now registered BRAF inhibitor vemurafenib, which was registered in Australia in May 2012. Although this agent was not registered at the time of design and implementation of the studies, it has now become standard of care for BRAF V600 mutation positive metastatic melanoma patients (superseding dacarbazine) according to the NCCN Guidelines (Version 1.2013). Therefore, an assessment should also be made of the efficacy of dabrafenib compared to vemurafenib.

The pivotal study supporting the efficacy of vemurafenib was in 675 treatment naive patients with predominantly BRAF V600E mutation-positive unresectable or metastatic melanoma, comparing treatment with either vemurafenib or dacarbazine[12, 13]. The co-primary outcomes were OS and PFS. Those treated with vemurafenib had a median OS of 13.2 months (compared to 9.6 months with DTIC), and a median PFS of 5.3 months (compared to 1.6 months with DTIC). The dabrafenib PFS results from the BREAK-3 study (5.1 months) compare favourably, however as the OS data for this study are not yet mature, it was not possible to compare OS results. Moreover, the allowance for treatment crossover on disease progression in the BREAK-3 study is likely to confound the OS results. Therefore, based on the currently available pivotal study results, there is no obvious difference in efficacy between dabrafenib and vemurafenib, although no head-to-head comparison exists to determine the superiority of one treatment over the other.

Comparison of dabrafenib with ipilimumab is less relevant to the registration of dabrafenib due to being of a different class with a different mode of action. Ipilimumab has been registered for the second-line treatment of advanced or metastatic melanoma in Australia since June 2011, and similar to vemurafenib, is recommended as a first line treatment against advanced or metastatic melanoma by the NCCN Guidelines (Version 1.2013). Ipilimumab acts indirectly by enhancing a T-cell mediated immune response against tumours. In the pivotal study supporting the efficacy of ipilimumab, the medial OS was 10 months in subjects given one course of ipilimumab compared to 6 months in the control group. As the data for OS in the BREAK-3 study are not yet mature, no comparison can be made. It is noted that the clinical summary stated that the BREAK-2 study found an OS of 13.1 months at 12 months follow-up, but as discussed in Section 7.1.2.1 no data was available in the submission to verify this figure. Again, no head-to-head data was provided to compare the efficacy of dabrafenib with ipilimumab. Ipilimumab has an advantage over dabrafenib and vemurafenib in that its efficacy is not limited to patients with BRAF V600 mutations. However, there are substantial safety concerns with its use which are discussed in Section 8.9.

[12] Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *New Engl J Med.* 2011;364(26):2507-2516

[13] Chapman PB, Hauschild A, Robert C, et al. Updated overall survival (OS) results for BRIM-3, a phase III randomized, open-label, multicenter trial comparing BRAF inhibitor vemurafenib (vem) with dacarbazine (DTIC) in previously untreated patients with *BRAFV600E*-mutated melanoma. 2012 ASCO Annual Meeting. *J Clin Oncol* 30, 2012 (suppl; abstract 8502).

7.2.5. Data limitations

The exclusion from the pivotal BREAK-3 study of subjects with brain metastases and BRAF V600K mutations precludes confident generalisation of the study results to these populations. Although these two factors were addressed in the supporting BREAK-2 and BREAK-MB studies, the Phase II nature of these studies impacts on their generalisability. This has implications for assessing the likely efficacy of dabrafenib in the intended patient population of those with advanced or metastatic BRAF V600 mutation positive unresectable or metastatic melanoma, with CNS metastases and V600K mutations affecting up to 75% and 20% of this target population respectively[14]. Reduced efficacy of dabrafenib in these patient sub-groups may dilute the impact of treatment in the intended population, resulting in a reduced efficacy than was observed in the BREAK-3 trial.

Another limitation of the data includes the lack of non-white patients in the trial populations, meaning that the efficacy of dabrafenib in other racial groups remains unknown.

Differences in the formulation of dabrafenib in the BREAK-2 study (gelatine capsules) compared to that used in the BREAK-3 and BREAK-MB study and proposed for registration (HMPC capsules) are likely to have reduced the amount of pharmacologically active dabrafenib used in the BREAK-2 study, and therefore will not have affected the validity of the efficacy results (although this may have impacted on safety observations).

It is also noted that there are other forms of BRAF V600 mutations that occur infrequently (for example, V600D). No data was submitted examining the efficacy of dabrafenib in these subtypes, and therefore no evaluation assessment can be made.

8. Clinical safety

8.1. Studies providing evaluable safety data

8.1.1. Integrated safety population

An Integrated Summary of Safety (ISS) was provided with the application, which comprised the Clinical Summary of Safety in Module 2. This integrated analysis combined the safety results from the studies: BRF113683 (BREAK-3); BRF11392 (BREAK-MB); BRF113710 (BREAK-2); BRF113220 (dabrafenib and trametinib); and BRF112680 (FTIH). The safety results in the integrated dabrafenib safety population (N=578) were evaluated for consistency against the dabrafenib-treated subjects (N=187) in the pivotal BREAK-3 study. Due to differences in assessment schedules across the 5 studies, integrated safety data were not summarised by time point. Integrated summaries of safety display baseline and worst-case on-therapy results only. In general, the baseline characteristics of the integrated safety population were similar to that of the dabrafenib arm of the BREAK-3 study: mean and median age both 53.0 years, 61% male, and >95% White. Throughout this CER, the results of the ISS are presented where relevant alongside the results of the pivotal study BREAK-3.

In addition to the integrated safety population, the following individual studies provided evaluable safety data:

8.1.2. Pivotal efficacy studies

In the pivotal efficacy study BRF113683 (BREAK-3), the following safety data were collected:

- General adverse events (AEs) were assessed by regular safety assessments including physical examinations, vital signs, dermatologic exams, laboratory measurements (e.g.,

[14] Jakob JA, Bassett RL, Ng CS, et al. NRAS mutation status is an independent prognostic factor in metastatic melanoma. *Cancer*. 2011: doi: 10.1002/cncr.26724

haematology, serum chemistry, urinalysis, pregnancy tests), electrocardiograms (ECGs), and echocardiograms (ECHO) for determination of LVEF and assessment of valvular morphology, at specified time periods. It was reported that AEs and serious adverse events (SAEs) were monitored continuously.

Comment: Although 'continuous monitoring' of AEs and SAEs was reported, there was no information within the CSR or Study Protocol for Study BRF113683 describing the methods by which details of these AEs were elicited (e.g. by specific or open-ended questioning). Without these details it is difficult to assess the completeness of data collection, underreporting of AEs cannot be excluded.

- AEs of particular interest, including pre-malignant and malignant skin lesions; treatment-emergent malignancies; pyrexia; abnormal ejection fraction; cardiac valvular abnormalities; uveitis; neutropenia; and renal failure, were assessed by regular physical examinations, dermatologic exams, echocardiograms, and laboratory tests accompanying study visits.
- Laboratory tests, including clinical chemistry, haematology, liver and renal function, were performed at baseline and then three-weekly intervals.
- ECGs were performed at baseline, Weeks 3, 6 and 12, and then at 9 weekly intervals thereafter during study treatment.
- Echocardiograms were performed at baseline, Weeks 6 and 12, and then at 9 weekly intervals thereafter during study treatment.

8.1.3. Pivotal studies that assessed safety as a primary outcome

Not applicable.

8.1.4. Dose-response and non-pivotal efficacy studies

The dose-response and non-pivotal efficacy studies provided safety data, as follows:

- Study BRF113710 (BREAK-2) provided data on general AEs and AEs of particular interest. These were collected by physical examination and AE questioning (baseline, Weeks 3, 6, 9, 12 and then 4 weekly thereafter), radiological lesion assessments (baseline, Weeks 6, 12 and then 8 weekly until Week 52), laboratory tests (baseline, Weeks 3, 6, 9, 12 and then 4 weekly thereafter), ECG (baseline, Weeks 3, 6, 12 and then 8 weekly until Week 52), and echocardiogram (baseline, Weeks 6, 12 and then 8 weekly until Week 52).

Comment: As previously noted, the formulation of dabrafenib used in the BREAK-2 study (as gelatine capsules) differs from that used in the pivotal trial and proposed for registration (HPMC capsules). As the effect of gelatine capsules was to reduce dabrafenib's bioavailability (see Section 4.2.2.2.3), the safety results from the BREAK-2 study may underestimate the adverse effects compared to the HPMC formulation. See Sections 3.2 and 8.8.3 for further discussion.

- Study BRF113929 (BREAK-MB) provided data on general AEs and AEs of particular interest. AE questioning and laboratory monitoring occurred at baseline and then at 4 weekly intervals during study treatment. Physical examination occurred at baseline, Weeks 1, 4 and then at 8 weekly intervals thereafter. Radiological, neurological and skin lesion assessment occurred at baseline, Weeks 4 and 8, and then at 8 weekly intervals thereafter. ECG monitoring and echocardiogram were performed at baseline, Week 4, and then 8 weekly thereafter.

8.1.5. Other studies evaluable for safety only

8.1.5.1. Study BRF113220

Study BRF113220 is an ongoing multi-centre, open-label, dose-escalation Phase I/II study, that was designed as a 4-part study to investigate the safety, PK, PD and clinical activity of

dabrafenib in combination with trametinib in subjects with BRAF mutant metastatic melanoma. Subjects were excluded if they had prior exposure to BRAF or MEK inhibitors and prior anti-cancer therapy in the metastatic setting, with the exception of up to one regimen of chemotherapy and/or interleukin-2. A synoptic report was provided presenting preliminary safety data from the dabrafenib monotherapy arm of Part C of the study as of the data cut-off date of 01 September 2011. 53 subjects were included in this arm and received 150mg of dabrafenib (gelatine capsules) BID for a median duration of 3.81 months. At the time of data collection 46/53 subjects (87%), were ongoing in the monotherapy arm of Part C of the study. In terms of baseline characteristics, the median age was 50 years, 100% were White, 44/53 subjects (83%) had the BRAF V600E mutation and 9 (17%) had the BRAF V600K, and all subjects had ECOG scores of 0 or 1. Data presented included exposure, AEs (including SAEs, fatal AEs, AE leading to discontinuation or dose interruption, AEs of special interest), clinical laboratory tests, ECG, and ECHO findings. Other safety data for dabrafenib use in combination with trametinib in other arms of the study was not evaluated due to potential confounding from the use of trametinib. No other study data (relating to efficacy, PK or PD) was provided within the synopsis for evaluation (although an interim PK report from this study was provided separately).

8.1.5.2. Study BRF113928

This was a Phase II study of dabrafenib 150mg BID in subjects with advanced non-small cell lung cancer and BRAF mutations. The study is ongoing with 5 of a planned 40 subjects enrolled at the time of reporting. Only a Short Study Summary and SAE listing was provided with the submission. One subject reported a SAE of blisters, and this narrative was included in the submission (see Section 8.4.2.1.2).

8.1.5.3. Study BRF114144

This is a Phase I, multicenter, non-randomized, open-label rollover study to provide continued treatment with dabrafenib to subjects with BRAF mutation-positive tumours who have completed previous dabrafenib investigational studies and are still receiving benefit. As of the 30 March 2012 data cut-off, 98 subjects were enrolled, all of whom had been in early phase and clinical pharmacology studies. Only a Short Study Summary and SAE listing was provided with the submission, with no analysis or grouping of AEs more generally (see Section 8.4.3.1.2).

8.1.6. Clinical pharmacology studies

8.1.6.1. Study BRF112680

In general, the safety findings in this study were consistent with those of the studies outlined in this section. This study was a dose-finding study, with multiple cohorts of subjects administered different doses of dabrafenib. In general, the incidence of serious adverse events was greater with higher doses of dabrafenib, and in particular the AEs of headache, pyrexia, rash, hyperkeratosis, and chills would appear to be dose-related.

8.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

8.3. Patient exposure

See Table 11 and Table 12 and for summaries of patient exposure across studies.

In the pivotal study, BRF113683 (BREAK-3), 187 subjects were allocated to dabrafenib in the randomised phase, with a mean and median daily dose of 284.9 mg and 300 mg, respectively, and a median duration on study treatment of 4.9 months. The mean and median dose intensity of DTIC was 311.6 mg/m^2/week and 332.0 mg/m^2/week, respectively, with a median duration on study treatment of 2.8 months. In the crossover phase, 28 subjects were exposed to

dabrafenib with a mean and median daily dose of 292.6 mg and 300 mg, respectively, and a median duration on crossover study treatment of 2.8 months.

In Study BRF113710 (BREAK-2), there were 92 subjects, with mean and median daily dose of dabrafenib being 282.4 mg and 300 mg, respectively, and a median duration on study treatment of 4.8 months.

In Study BRF113929 (BREAK-MB), there were 172 subjects in total. This consisted of 89 subjects in Cohort A, with mean and median daily dose of dabrafenib of 280.3 mg and 300 mg respectively and a median duration on study treatment of 3.9 months, and 83 subjects in Cohort B, with a mean and median daily dose of dabrafenib of 281.6 mg and 298.7 mg respectively and a median duration on study treatment of 4.0 months.

In the dabrafenib monotherapy arm of Part C in Study BRF113220, there were 53 subjects with a mean and median daily dose of dabrafenib of 295.95 mg and 299.12 mg respectively, and a median duration on study treatment of 3.81 months. No data was provided on individual duration of dabrafenib treatment in this study for input into Table 12.

In Study BRF113928, 5 subjects were enrolled at the time of reporting. No details on duration of treatment were provided.

In the integrated safety population, exposure was similar to the dabrafenib arm in the BREAK-3 study, with a mean and median daily dabrafenib dose of 284.8 mg and 300 mg respectively, and a median time on study treatment of 4.62 months.

From Table 12 it can be seen that there is limited data on the safety of dabrafenib with long-term use, with only 5 subjects providing safety data at the proposed dose range for more than 12 months.

Comment: Limited numbers of long-term follow up is acceptable in light of the generally poor prognosis of the target population, and therefore reduced likelihood of survival beyond 12 months.

Table 11. Exposure to dabrafenib and comparators in clinical studies.

Study type/Indication	Controlled studies			Uncontrolled studies	Total dabrafenib
	Dabrafenib	Placebo	DTIC	dabrafenib	
Clinical pharmacology					
BRF112680				184*	184
Stage III & IV melanoma, treatment naive					
Pivotal BREAK-3	187	-	59		187
Stage III & IV melanoma, dabrafenib crossover from DTIC or previous other treatment					
Pivotal BREAK-3				28	28
BREAK-2				92*	92
BRF113220				53*	53

Study type/Indication	Controlled studies			Uncontrolled studies	Total dabrafenib
	Dabrafenib	Placebo	DTIC	dabrafenib	
Melanoma CNS metastases					
BREAK-MB				172	172
Other cancer indications					
BRF113928				5	5
Rollover BRF114144				98*	98
TOTAL	187		59	632	819

Table 12. Exposure to dabrafenib in clinical studies according to dose and duration: proposed dose range = proposed maximum dose = 150mg BID.

Study type/Indication	Proposed dose range = Proposed maximum dose			
	≥ 3 mo.	≥ 6 mo.	≥ 12 mo.	Any duration
Clinical pharmacology				
BRF112680	53*	30*	5*	70*
Stage III & IV melanoma, treatment naive				
Active-controlled BREAK-3	154	49	0	187
Subtotal Indication 1				
Stage III & IV melanoma, dabrafenib crossover from DTIC or previous other treatment				
Uncontrolled BREAK-3 crossover	13	2	0	28
Uncontrolled BREAK-2	69*	40*	0	92*
Uncontrolled BRF113220	n/a	n/a	n/a	53*
Subtotal Indication 2				
Melanoma CNS metastases				
Uncontrolled BREAK-MB	116	40	0	172

Study type/Indication	Proposed dose range = Proposed maximum dose			
	≥ 3 mo.	≥ 6 mo.	≥ 12 mo.	Any duration
Subtotal Indication 2				
Other cancer indications				
Uncontrolled BRF113928	n/a	n/a	n/a	5
Uncontrolled Rollover BRF114144	n/a	n/a	n/a	98*
Subtotal Indication 2				
TOTAL	405	161	5	705

* Gelatine capsules: Note different drug formulations in different studies and impact on development of AEs.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Pivotal study BREAK-3 and ISS

The majority of subjects in both treatment arms in Study BRF113683 (BREAK-3) experienced at least one AE (185/187 or 99% in the dabrafenib arm, and 54/59 or 92% in the DTIC arm). The most common AEs reported in the dabrafenib arm were hyperkeratosis (37%), headache (32%), pyrexia (28%), arthralgia (27%), skin papilloma (24%), alopecia (22%) and palmar-plantar erythrodysaethesia (PPE) syndrome (20%), which were all reported more frequently than in the DTIC arm. Adverse events typically expected with cytotoxic chemotherapy including GI symptoms (nausea, vomiting, abdominal pain) and cytopenias (including neutropenia, anemia and thrombocytopenia) were more common in the DTIC arm than in the dabrafenib arm. Fatigue and asthenia were common in both arms of the study. Grade 3 events were reported at a similar frequency in both arms (29% in the dabrafenib arm and 27% in the DTIC arm), while Grade 4 AEs were experienced by 4% of subjects in the dabrafenib arm and 14% of subjects in the DTIC arm. The most common Grade 3 and 4 AEs in the dabrafenib arm were pyrexia (3%) and PPE syndrome (2%). One subject in each treatment group reported a Grade 5 (fatal) AE, however neither of these was assessed as being related to study treatment.

The most common AEs for crossover phase subjects appeared to be similar to those reported by subjects receiving dabrafenib in the randomised phase, however small numbers and limited duration of follow-up prevented meaningful interpretation.

Comment: The results indicate that the profile of adverse effects for dabrafenib is distinctly different to that of DTIC. Generally the AEs associated with dabrafenib appear to have less systemic involvement, and therefore have a lesser impact on quality of life. As the dosage and formulation of dabrafenib used in this study (150mg BID HPMC capsules) is that same as that proposed for registration, it would seem that the proposed regimen as a tolerable and manageable safety profile compared to the standard of care DTIC treatment.

8.4.1.1.1. Integrated safety population

The overall experience of AEs was similar in the integrated safety population to the dabrafenib arm of the BREAK-3 study. 96% of subjects in the integrated safety population experienced any AE, and the AE profile was similar to the dabrafenib arm of the BREAK-3 study, although generally with slightly reduced frequency: hyperkeratosis (29%), headache (28%), pyrexia (26%), arthralgia (25%), fatigue (25%), nausea (22%) and skin papilloma (20%).

Comment: The lower frequency of AEs observed in the integrated safety population compared to the pivotal BREAK-3 study could be explained in part by the inclusion of studies in which dabrafenib was administered as gelatine capsules. As gelatine capsules have a lower bioavailability, this could have the effect of decreasing the rate of adverse events that are observed in these populations.

8.4.1.2. Other studies

In study BRF113710 (BREAK-2), 86/92 (93%) of subjects experienced any AE, the most common being arthralgia (33%), hyperkeratosis (27%), pyrexia (24%), fatigue (22%), headache (21%) and nausea (20%). The AE profile was similar to that of the pivotal study BREAK-3. 27% of subjects experienced a maximum Grade 3 AE, while 9% of subjects experienced a maximum Grade 4 AE.

In study BRF113929 (BREAK-MB), 158/172 (92%) of subjects experienced at least one AE, with 40% experiencing a Grade 3 or 4 AE. The most common AEs were headache (28%), hyperkeratosis (26%), nausea (26%), pyrexia (26%), fatigue (25%) and vomiting (20%). AEs that occurred more frequently (≥10% higher) in Cohort B (prior local therapy for brain metastases) than Cohort A (no prior local therapy for brain metastases) included nausea (33% vs. 19%), fatigue (30% vs. 20%), diarrhoea (18% vs. 8%) and constipation (13% vs. 3%). Due to CNS involvement, nervous system disorders were also of special interest in this study, which were observed in 42/89 (47%) subjects in Cohort A, and 42/83 (51%) subjects in Cohort B. In all, 16/172 (9%) subjects experienced a Grade 3 or Grade 4 nervous system AE, and 3/172 (2%) subjects experienced a Grade 5 nervous system AE. CNS haemorrhage was observed in 10 subjects (5 from each cohort), and all were deemed not related to study treatment.

Comment: The all AE profile in the supporting studies (BREAK-2 and BREAK-MB) is generally consistent with that seen in the pivotal study BREAK-3. However, there are observed lower rates of hyperkeratosis (27% in BREAK-2 and 26% in BREAK-MB compared to 37% in BREAK-3) and skin papilloma (15% in both BREAK-2 and BREAK-MB compared to 24% in BREAK-3).

In the dabrafenib monotherapy arm of Part C in Study BRF113220, 53/53 subjects (100%) experienced at least one AE, with the most common being fatigue (40%), alopecia (32%), rash (30%), headache (26%), arthralgia (26%), diarrhoea (26%), hyperkeratosis (26%), and myalgia (23%). AEs of Grade 3 or 4 were observed in 36% subjects.

8.4.2. Treatment-related adverse events (adverse drug reactions)

8.4.2.1. Pivotal study BREAK-3 and ISS

In the BREAK-3 study, a greater proportion of subjects in the dabrafenib arm experienced AEs considered related to study treatment than in the DTIC arm (88% compared to 73% respectively). The most common drug-related events in the dabrafenib arm were hyperkeratosis (34%), skin papilloma (21%), alopecia (20%), PPE syndrome (19%), fatigue (17%), headache (17%), arthralgia (16%), rash (16%), pyrexia (15%), asthenia (14%), and nausea (10%).

Certain AEs were identified as events of special interest because of their presumed relationship to dabrafenib or other kinase inhibitors observed in clinical or preclinical studies. These included:

- Premalignant and malignant skin lesions – these had been reported as a possible class effect of BRAF inhibitors, from studies with vemurafenib and earlier dabrafenib studies. In the dabrafenib arm, 9/187 (5%) subjects reported cutaneous squamous cell carcinoma (SCC) with a median time to onset of 12 weeks. All cases were considered to be related to dabrafenib treatment, and were treated with surgical curettage and reported as resolved without dose modification. SCC was reported in 3/28 (11%) subjects in the crossover population with a median time to onset of 9 weeks. Again all were treated with surgical curettage and reported as resolved without dose modification. No subjects in the DTIC arm were observed to experience SCC. Actinic keratosis was observed in 12/187 (6%) subjects in the dabrafenib arm, 2/28 (7%) in the crossover phase, and no subjects in the DTIC arm. Keratoacanthoma was experienced by 5/187 (3%) subjects in the dabrafenib arm, 1 subject in the crossover phase, and no subjects in the DTIC arm.

  In the integrated safety population, 52/578 (9%) subjects reported events of premalignant and malignant skin lesions, with approximately 67% of these events occurring in the first 12 weeks of treatment (median time to onset 8 weeks). Cumulative incidence appeared to plateau around 32 weeks. There were no fatal events, no subject required permanent discontinuation from treatment, and 90% of cases were resolved.

Comment: These results indicate that use of dabrafenib increases the risk of premalignant and malignant skin lesions. This is in keeping with the results from vemurafenib studies, and therefore point to this being a class-effect of BRAF inhibitors. Cases of cutaneous SCC reported in the BREAK-3 study were detected early with regular dermatologic screening, and the cumulative incidence in the integrated safety population appears to plateau. Therefore, early and frequent dermatologic monitoring is warranted with dabrafenib use. However, the long term effects of dabrafenib on the rate and severity/aggressiveness of cutaneous malignancies are not known in light of limited follow-up duration, and the continued monitoring and reporting of these events would be of benefit.

- Other malignancies - Other treatment-emergent primary malignancies were observed in 9/187 (5%) subjects in the dabrafenib arm, including 3 subjects with new primary melanomas, 5 subjects with basal cell carcinomas (BCC) and 1 subject with mycosis fungoides, while no cases of other treatment-emergent primary malignancies were experienced in the DTIC arm.

- In the integrated safety population, treatment-emergent malignancies were observed in 20/578 (3%) subjects, of which 13 subjects (65%) had BCC and 5 subjects (25%) had new primary melanoma. All were treated with surgical excision without the need for permanent discontinuation of treatment.

Comment: As suggested in the ISS, these figures are in keeping with (or lower than) studies in the general population which have found a risk of up to 6% of subsequent primary melanoma diagnosis in melanoma patients within the first post-diagnosis year[15]. Therefore, the current data does not suggest an association between use of dabrafenib and the development of other malignancies (other than SCC or keratoacanthoma), although these should still be monitored with continued follow-up. No data was presented on the underlying rate of subsequent BCC in melanoma patients, however the rate observed in this study does not appear to be high.

- Pyrexia - Early studies of dabrafenib indicated that pyrexia was one of the most frequently occurring AEs (Study BRF112680: 34%; BRF113710: 24%). It was reported that the

[15] Titus-Ernstoff L, Perry AE, Spencer SK, et al. Multiple primary melanoma: two-year results from a population-based study. *Arch Dermatol.* 2006;142(4):433-8.

aetiology of this phenomenon remains unclear and is under investigation. During the randomised phase of the BREAK-3 study, 53/187 subjects (28%) in the dabrafenib arm and 6/59 subjects (10%) in the DTIC arm experienced pyrexia. Of those with an event in the dabrafenib arm, pyrexia was considered possibly related to dabrafenib in 29/53 subjects (55%), and was considered a SAE in 7/53 subjects (13%). Of all episodes, the maximum Grade was Grade 1 in 25/53 (47%) subjects, Grade 2 in 22 (42%) subjects, and Grade 3 in 6 (11%) subjects. There were no Grade 4 events. 27 subjects (51%) who experienced pyrexia had an event within 2 weeks of beginning treatment with dabrafenib and most (75%) of events lasted ≤5 days, with a mean duration of 5.7 days. Treatment with dabrafenib was interrupted for 20 subjects (38%) and the dose reduced for 16 subjects (30%), but was unchanged for 66%. Events in most subjects (98%) resolved. Pyrexia was observed in 7/28 subjects (25%) in the crossover phase, of which 1 was considered a SAE, and all recovered without the need for drug withdrawal. 2 subjects were identified in the study cohort as having serious non-infectious febrile events.

Comment: Although most episodes of pyrexia were of low grade and resolved, it is noted that a substantial proportion of events were considered SAEs (13%) compared to no SAEs in the DTIC arm. Although most cases of pyrexia were of short duration, 5/53 subjects (9%) had events lasting >10 days, and case reports indicated that fever reached as high as 40.2°C.

The investigators assessed only 55% of pyrexia episodes on dabrafenib as being related to study drug, however this assessment is questionable as the remaining episodes still represent a higher frequency than is observed in the DTIC arm. No case histories of pyrexia episodes (other than those classified as SAEs) were provided to verify the assessments.

Therefore, the study results suggest that AE of pyrexia is associated with treatment with dabrafenib, and has the potential to be severe and have significant impacts on other organ systems and overall functioning.

In the integrated safety population, 154/578 (27%) subjects reported AEs of pyrexia, of which 64% were considered to be related to study treatment. 27/154 (18%) were considered SAEs, and 98% resolved. 25/154 (16%) subjects required dose reduction due to pyrexia and 34% required dose interruption, however no subjects needed permanent withdrawal from study treatment. The mean and median time to first occurrence was 6.2 and 3 days respectively, and the mean and median duration of first occurrence was 5.3 and 3 days respectively.

- Abnormal ejection fraction - Left ventricular ejection fraction (LVEF) changes were not reported to be observed in early safety reviews of dabrafenib, however were included in AEs of special interest because they are known side effects of several kinase inhibitors and are potentially life-threatening. In all, 97/187 subjects (54%) in the dabrafenib arm had an investigator-assessed decrease in LVEF from baseline compared to 27/59 subjects (52%) in the DTIC arm. In the dabrafenib arm, 19/187 subjects (10%) had a ≥ 10% decrease in LVEF, compared to 2/59 subjects (4%) in the DTIC arm, and of these, 4/187 (2%) in the dabrafenib arm had LVEF fall to below the lower limit of the normal range compared to none in the DTIC arm.

Comment: These results suggest that there was a greater degree of LVEF decrease for subjects in the dabrafenib arm compared to DTIC, and therefore, there may be an association between treatment with dabrafenib and reductions in LVEF which may be of clinical significance and warrants monitoring.

In the integrated safety population, 6/578 subjects (1%) were reported to experience an AE of ejection fraction decreased, 4 of which were considered to be SAEs, however, data was

not provided to evaluate the proportion of subjects who experienced any decrease in LVEF from baseline.

- Cardiac valvular abnormalities – Echocardiograms were used to monitor for cardiac valve abnormalities, based on data from preclinical studies in which hypertrophy of the tricuspid valve was observed in a dog (see Section 5.2.2.2). Three subjects (2%) in the dabrafenib arm experienced cardiac valvular abnormalities, of which two were assessed as possibly related to the study treatment. One subject was shown to develop moderate thickening of the aortic valve while on treatment, which had been normal at baseline. This was compared to no cases of cardiac valvular abnormalities in the DTIC arm.

Comment: These results suggest that there may be an association between treatment with dabrafenib and cardiac valvular abnormalities, consistent with the findings from the preclinical studies. As these events are rare, further follow up may be required to assess the extent of any association, and this is warranted in light of the potentially significant adverse sequelae.

No additional cases of valvular disease AEs were identified in the integrated safety population. The Sponsor stated that due to the infrequent nature of these events, valvular abnormalities are no longer considered an AE of special interest for dabrafenib requiring inclusion in the RMP.

Comment: As detailed in the previous comment, the opinion of this evaluator is that an association between use of dabrafenib and cardiac valvular abnormalities cannot be excluded due to this being a rare occurrence and the relatively limited follow up to date. Therefore, at odds with the Sponsor, the opinion of this evaluator is that ongoing monitoring for valvular abnormalities and its and inclusion in the RMP may still be warranted.

- Uveitis – This was monitored following an observed increased frequency of uveitis with the BRAF inhibitor vemurafenib. Only one subject in the dabrafenib arm experienced uveitis, which was Grade 1 and resolved spontaneously. No cases of uveitis were experienced in the DTIC arm. In the integrated safety population, there were 5/578 subjects (<1%) who experienced uveitis or iritis, none of which required discontinuation of treatment, although 4 of the cases were considered to be possibly related to dabrafenib treatment.

- Neutropenia - Severe neutropenia was observed in 1 subject (<1%) in the dabrafenib arm and 9 subjects (15%) in the DTIC arm. No cases of severe neutropenia were experienced in the crossover phase. In the integrated safety population, 6/578 subjects (1%) experienced Grade 3 or 4 events of neutropenia.

Comment: Although events of severe neutropenia were not commonly observed, lower grade events of neutropenia were observed more frequently (see Section 8.5.4.1.1). Therefore, although less severe than with DTIC, there still appears to be an effect of dabrafenib on neutrophil levels that may warrant monitoring.

- Renal failure - As of the data cut-off, no subjects experienced renal failure in either the randomised phase or crossover phase, and there were no Grade 3 or Grade 4 elevations in creatinine.

  In the integrated safety population, 4/578 subjects (<1%) experienced AEs of renal failure, of which two were reported as SAEs and one was considered related to study treatment. All cases were managed with dose modification.

Comment: Although uncommon, the observation of sporadic cases of acute renal failure in the dabrafenib studies (see Section 8.5.2) warrants appropriate renal monitoring and precautions with its use.

- Palmar-Plantar Erythrodysesthesia (PPE) – This was observed in 20% of subjects in the dabrafenib arm of the BREAK-3 study, and in 13% of the integrated safety population. Most cases were of low grade, with 2% in the BREAK-3 study and 1% in the integrated safety population being Grade 3, and no Grade 4 cases.
- Phototoxicity - The conclusion if the BREAK-3 CSR states: 'The incidence of phototoxicity in this study was low, and higher in the DTIC arm (8%) than the GSK2118436 arm (3%). Phototoxicity does not appear to be a class effect, as reported rates for GSK2118436 are less than literature reports for vemurafenib (33%).'

Comment: Apart from in the conclusion as quoted above, there is no reference to phototoxicity within the report body of BREAK-3 CSR or in the ISS. Therefore, the accuracy of this claim cannot be verified in this evaluation. As photosensitivity is a documented AE of the BRAF inhibitor vemurafenib, more details on the data supporting this claim would be useful.

8.4.2.2. Other studies

In Study BRF113710 (BREAK-2), the most common AEs considered to be related to dabrafenib were arthralgia (28% subjects), hyperkeratosis (24%), fatigue (16%), nausea (16%), skin papilloma (15%), headache (13%), pain in extremity (11%), and pyrexia (11%). In terms of AEs of special interest, 9/92 subjects (10%) experienced SCC of the skin, 7 subjects (8%) experienced actinic keratosis, 1 subject (1%) experienced keratoacanthoma, 4 subjects (4%) experienced other treatment-emergent malignancies (including BCC and AML). All but one skin malignancy was considered to be related to study treatment. 22 subjects (24%) experienced pyrexia (considered to be related to study treatment in 10 subjects), with one subject identified as possibly having a non-infectious febrile event. There was a ≥10% decrease in LVEF in 12 subjects (14%), with a fall below the LLN in one of these subjects (although the LVEF in 3/46 subjects (7%) was assessed to fall below the LLN with independent assessment). No reports of cardiac valvular abnormalities were reported by the investigators, although some abnormalities were detected on blinded central analysis, the significance of which is uncertain. Uveitis was observed in 1 subject, there were no cases of Grade 3 or 4 neutropenia, and there was one report of acute renal failure (ARF) which was considered to be related to dabrafenib use (see Section 8.5.2.1.2 for more details).

Comment: The findings from the BREAK-2 study would seem consistent with that of the pivotal study BREAK-3, keeping in mind the reduced dabrafenib exposure in this study due to the use of gelatine capsules. In line with these findings, the abnormal ejection fraction is an AE that could potentially be related to dabrafenib use.

In Study BRF113929 (BREAK-MB), the most common AEs considered related to study treatment were hyperkeratosis (23%), fatigue (19%), pyrexia (19%), rash (16%), PPE syndrome (15%), skin papilloma (13%) and alopecia (13%). In terms of AEs of special interest, 11/172 subjects (6%) experienced cutaneous SCC, 9 subjects (5%) experienced actinic keratosis, 1 subject (1%) experienced keratoacanthoma, and 3 subjects (2%) experienced the other treatment-emergent malignancy of BCC. Of the above skin lesions, all but 2 were considered related to dabrafenib. 44 subjects (26%) experienced pyrexia, which was considered treatment related in 32/44 (73%) and serious in 10/44 (23%), and all episodes resolved without the need for permanent treatment discontinuation. 2 subjects were identified as having experienced a serious non-infectious febrile event. There was a ≥10% decrease in LVEF in 21 subjects (13%), with a fall below the LLN in 2 of these subjects. It was reported that no cardiac valvular abnormalities were reported in either patient with LVEF events, however no information was provided for other study subjects within the CSR. Grade 4 neutropenia was experienced by 3 subjects (2%), of which 2 required dose interruption/reduction, however all resolved without the need for permanent discontinuation of dabrafenib. 2 subjects experienced Grade 3 pancytopaenia which

included decreased neutrophils, which led to permanent discontinuation of dabrafenib in one of these subjects. Uveitis was experienced by 2 subjects (1%), and acute renal failure was reported in 2 subjects (1%), with both episodes considered unrelated to treatment.

Comment: The absence of cardiac valvular ECHO results prevents assessment of cardiac valvular AEs in the BREAK-MB study. The results of this study indicate a possible association between dabrafenib use and severe neutropenia which warrants monitoring. On review of the case histories, it is the opinion of this evaluator that one of the cases of acute renal failure could possibly be associated with dabrafenib treatment based on the information provided.

In the dabrafenib monotherapy arm of Part C in Study BRF113220, 49/53 subjects (92%) had AEs that were considered drug-related by investigators. The most frequently reported drug-related AEs were fatigue and rash (both 30%), alopecia (28%), hyperkeratosis (23%), arthralgia and diarrhoea (both 19%), myalgia (17%), pyrexia, chills, nausea, pruritis and PPE (all 15%). In terms of AEs of special interest, 9 (17%) subjects experienced pyrexia, 7 (13%) experienced cutaneous SCC, 4 (8%) had keratoacanthoma, 2 (4%) had actinic keratosis, 1 (2%) had BCC, and 1 (2%) had cutaneous SCC. It was reported that as of the clinical cut-off date, no cases of uveitis, cardiac valvular abnormalities, abnormal ejection fraction, neutropenia or renal failure were reported in the 53 subjects randomised into the dabrafenib monotherapy arm in Part C of the study. However, it was recorded that 9/53 subjects (17%) had ≥10% decrease in LVEF, and 4 subjects (8%) had any grade decrease in neutrophils.

In ongoing Study BRF113928 in patients with advanced BRAF mutation positive non-small cell lung cancer, of 5 enrolled patients there was one reported SAE of clinically significant moderate phlyctena on the limbs immediately following administration of dabrafenib, which was repeated on rechallenge. Management was supportive. This was considered a reasonable possibility of being related to dabrafenib and treatment was discontinued.

Comment: The SAE observed of limb phlyctena would seem to be an acute reaction to dabrafenib treatment of clinical significance.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Pivotal study BREAK-3 and ISS

As of the data cut-off date in Study BRF113683 (BREAK-3), 21/187 subjects (11%) in the dabrafenib arm and 9/59 subjects (15%) in the DTIC arm had died. All but 1 death was attributed to the disease under study, with the additional death in the dabrafenib arm being due to elective euthanasia.

In the crossover population, one fatal SAE episode was observed resulting from hyponatremia, hypotension, sepsis and hypoxaemic respiratory failure, which was not assessed by the investigator to be caused by study treatment.

In the integrated safety population, 141/578 (24%) subjects had died, with disease under study reported as the primary cause of death in 137/141 (97%).

Comment: No case narratives were provided for all deaths that occurred in the BREAK-3 study. Therefore, the accuracy of death attribution to disease rather than treatment was not able to be verified.

A similar proportion of subjects in the BREAK-3 study experienced SAEs in both treatment groups: 23% in the dabrafenib arm compared to 22% in the DTIC arm. Serious AEs reported in more than 1% of the dabrafenib arm were SCC (5%), pyrexia (4%) and malignant melanoma (2%). The only SAE reported in more than 1 subject in the DTIC arm was abdominal pain.

These results were similar to that seen in the integrated safety population in which SAEs were reported for 150/578 subjects (26%), of which 96 (17%) were considered related to study treatment. The most frequent SAEs were SCC (6%), pyrexia (5%), and SCC skin (2%).

8.4.3.2. Other studies

In Study BRF113710 (BREAK-2), as of the data cut-off, 29 subjects (32%) had died, all of which were attributed to progression of disease under study, with no fatal SAEs. SAEs were experienced by 25/92 subjects (27%), with those reported in more than 1% of subjects including BCC (4%), SCC (4%), SCC of skin (4%), anaemia (3%), pyrexia (3%), non-cardiac chest pain (2%) and vomiting (2%).

In Study BRF113929 (BREAK-MB), as of the clinical cut-off date 73/172 (42%) of subjects had died (38/89 in Cohort A and 35/83 in Cohort B). The primary cause of death was disease progression in 71/73 subjects (97%), with the deaths for the other two subjects being attributed to 'other' and 'unknown'. Three subjects (2%) experienced fatal SAE of cerebral or intracranial haemorrhage, none of which were considered to be treatment-related by the investigator, with the primary cause of death considered to be disease under study (see comment below). SAEs were experienced by 51/172 (30%) subjects in the BREAK-MB study, of which 30/172 (17%) were considered to be treatment related. The most frequent SAEs were pyrexia (6%), intracranial haemorrhage (6%), and SCC (5%). SAEs were more frequent in Cohort B (35%) than Cohort A (25%).

Comment: It is noted that the death rate in the BREAK-2 study (32%) and the BREAK-MB study (42%) is higher than the rate observed in the pivotal BREAK-3 study (11%). Reasons for this could be more advanced disease in the latter 2 studies, which included previous treatment and subjects with brain metastases respectively. Case narratives for all deaths were again not provided in the CSRs, in order to verify the cause of death as being due to disease progression as reported, and it would be useful to have access to this information. This includes the two deaths classified as 'other' and 'unknown' in the BREAK-MB study.

One of the three deaths attributed to the SAE of cerebral haemorrhage in the BREAK-MB study was in a previously well-feeling subject with no prior local therapy, who deteriorated quickly and died of a cerebral haemorrhage within two days. This was considered likely due to haemorrhaging into a responding lesion in the brain. Although this death was attributed by the investigator to progressive disease, it is the opinion of this evaluator, that in this case, the cause may instead have been the (desired) effect of tumour shrinkage due to dabrafenib which precipitated the cerebral bleeding. Therefore, bleeding into responding CNS lesions may be an AE of dabrafenib in the setting of brain metastases which needs to be monitored.

The higher frequency of SAEs in Cohort B than in Cohort A, also points to a potential additive effect of previous local therapies on the risk of experiencing SAEs with dabrafenib use.

In the dabrafenib monotherapy arm of Part C in Study BRF113220, as of the clinical cut-off date, 6/53 subjects had died, all attributed to disease progression. 11/53 subjects (21%) experienced a SAE, the most common being cutaneous SCC observed in 5 (9%) subjects. All other SAEs were only observed in single subjects.

In the rollover study BRF114144, there were 5 deaths from 98 subjects at the time of data cut-off, all attributed to disease progression. SAEs were reported in 17/98 subjects (17%). SCC was observed as a SAE in 8 (8%) subjects, BCC, pyrexia and pneumonia were both observed in 2 subjects (2%), and there were single episodes of each of jaundice, granulomatous liver disease, and nephritis considered as a SAE.

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal study BREAK-3 and ISS

In Study BRF113683 (BREAK-3), treatment was permanently discontinued due to adverse events in 5/187 (3%) subjects in the dabrafenib arm, and 2/59 (3%) in the DTIC arm. This is comparable to the 10/578 (2%) of subjects in the integrated safety population who permanently discontinued treatment due to AEs.

Comment: Treatment discontinuation due to AEs was low in both study arms of the BREAK-3 study, and there was no predominant AE that led to treatment cessation in either the BREAK-3 study or the integrated safety population.

A similar proportion of subjects experienced AEs resulting in dose reductions in the dabrafenib and DTIC treatment arms in the BREAK-3 study (34/187 or 18%, and 10/59 or 17% respectively). The most common AEs resulting in dose reductions in the dabrafenib arm were pyrexia (9% of all dabrafenib subjects), PPE (3%), chills (3%), fatigue (2%) and headache (2%), while in the DTIC arm it was neutropenia (10%). Similarly, 51/187 (27%) subjects in the dabrafenib arm and 16/59 (27%) subjects in the DTIC arm experienced AEs resulting in dose interruptions/delays. The most common AE leading to dose interruption in the dabrafenib arm was pyrexia (11%), PPE (3%), and chills (3%), while in the DTIC arm it was neutropenia (14%) and thrombocytopenia (7%).

In the integrated safety population, 80/578 subjects (14%) had an AE leading to dose reduction, the most common being pyrexia at 4%, while 170/578 (29%) had an AE leading to dose interruption, the most common being pyrexia (9%), and hypophosphataemia, chills, vomiting and PPE syndrome (all 2%). This is in line with the findings of the BREAK-3 study.

8.4.4.2. Other studies

In Study BRF113710 (BREAK-2), 1 subject (1%) experienced an AE leading to permanent discontinuation of dabrafenib (AML). 13/92 subjects (14%) experienced AEs leading to dose reduction, with the most common AEs being hypophosphataemia (4%) and arthralgia (2%). 27/92 subjects (29%) experienced AEs resulting in dose interruptions, with the most common contributing AEs being hypophosphataemia (8%), arthralgia (4%), anaemia (3%), headache (3%) and pyrexia (3%).

In Study BRF113929 (BREAK-MB), 4/172 (2%) subjects discontinued study treatment due to AEs (2 cases of cerebral or intracranial haemorrhage, 1 case of lymphopaenia, and 1 case of pancytopaenia). 24 subjects (14%) experienced AEs that led to dose reductions, the most common being pyrexia (4%) and hypophosphataemia (2%). 55 subjects (32%) experienced AEs leading to dose interruptions, the most common being pyrexia (10%), vomiting (3%), chills (2%), hypotension (2%), decreased appetite (2%), and fatigue (2%). Again, dose reductions (16% vs.12%) and interruptions (40% vs. 25%) were more common in Cohort B than in Cohort A respectively.

Comment: Hypophosphataemia is noted as an AE that has led to dose reductions or interruptions in the supportive studies, and thus may warrant specific monitoring.

In the dabrafenib monotherapy arm of Part C in Study BRF113220, as of the data cut-off, no subject had AEs leading to discontinuation of therapy. 12/53 (23%) subjects had an AE leading to dose interruption, the most common cause being pyrexia which occurred in 2 (4%) subjects. 3 (6%) subjects had AEs leading to dose reductions.

One subject of 98 (1%) in the rollover study BRF114144 discontinued study treatment due to the adverse event of granulomatous liver disease, thrombocytopenia and renal insufficiency.

8.5. Laboratory tests

Data was provided for chemistry changes observed in the pivotal study BRF113683 (BREAK-3), for the supportive study BRF113710 (BREAK-2) and in the integrated safety population.

8.5.1. Liver function

8.5.1.1. Pivotal study BREAK-3 and ISS

In Study BRF113683 (BREAK-3), no subjects met laboratory criteria for possible Hy's law cases in either treatment group and no cases of possible hepatocellular injury were identified. Although it was reported that any grade increases in ALT (21/187 or 11%) and AST (15/187 or 8%) in the dabrafenib arm were lower than that observed in the DITC arm, it was noted that 2/187 subjects (1%) in the dabrafenib arm developed an increase in ALT or AST to Grade 3 compared to none in the DTIC arm. A similar low proportion of subjects in both treatment arms experienced Grade 1 or 2 elevations in bilirubin (2%), with no Grade 3 or 4 elevations observed.

In the integrated safety population, a slightly higher proportion of subjects were observed to have any grade increases in ALT (88/578 or 16%) and AST (73/587 or 13%), however the proportion who were observed to have Grade 3 increases were lower (<1%). No subjects in the integrated safety population met criteria for drug-induced liver injury of Hy's law.

Comment: Although no definitive cases of drug-induced liver injury have been reported, some low grade elevation in liver enzymes has been observed with dabrafenib use. Therefore, an effect of dabrafenib on liver function cannot be excluded, and further monitoring of liver enzymes with use may be warranted.

8.5.1.2. Other studies

In Study BRF113710 (BREAK-2), no possible Hy's law cases were identified. Although there were no cases of Grade 3 or above ALT or AST elevations, it is noted that there were 3/92 cases where the level of either reached >3x ULN. 3/91 subjects (3%) experienced a Grade 1 or 2 increase in bilirubin during study treatment. One possible case of hepatocellular injury was identified via laboratory markers, ALT (xULN)/ALP (xULN) ≥5, however, dabrafenib was continued, and this was reported to resolve without incident.

In Study BRF113929 (BREAK-MB), no cases of possible Hy's law were identified. Any Grade increases in ALT were seen in 21/165 (13%) subjects, of which 6/172 (3%) had an ALT elevation >3x ULN, and 2/172 (1%) had an ALT elevation >8x ULN. Any Grade increases in AST were seen in 23/165 (14%) subjects. Any Grade increases in bilirubin were seen in 4/163 subjects (2%), and in one subject there was an increase in bilirubin ≥2x ULN.

Comment: The results of the supportive studies are in line with the pivotal study indicating the potential for hepatocellular injury with dabrafenib use, and caution is required.

In the dabrafenib monotherapy arm of Part C in Study BRF113220, no subjects met the criteria for possible cases of Hy's law. One subject had elevated AST >3x ULN. 18/53 subjects (34%) had an any grade increase in GGT.

In the rollover study BRF114144, there was 1 subject of 98 (1%) who had granulomatous liver disease and jaundice, attributed by the investigator to be related to study treatment, and one additional patient who experienced jaundice as a SAE, not thought to be related to study treatment.

Comment: This finding in the rollover study (which was excluded from the integrated safety population) indicates a possible association between dabrafenib use and hepatic injury. This supports the need to monitor hepatic function while on treatment.

8.5.2. Kidney function

8.5.2.1. Pivotal study BREAK-3 and ISS

Kidney function was not specifically monitored in Study BRF113683 (BREAK-3) other than as part of routine laboratory monitoring. Elevations in serum creatinine from baseline were similar in both treatment groups (5%), and none were Grade 3 or 4 increases. In the integrated safety population, 35/578 (6%) subjects experienced at least one increase in serum creatinine as compared with baseline.

8.5.2.2. Other studies

In Study BRF113710 (BREAK-2), any grade increase in serum creatinine was observed in 11/91 subjects (12%), with one subject experiencing ARF with a creatinine increase to Grade 4. This occurred in a 79 year old subject, 218 days after the first dose of dabrafenib, which had been reduced to a dose of 75mg BID due to weight loss, fatigue and loss of appetite. The ARF improved with hospital treatment, but had not resolved completely at the time of data cut-off. Dabrafenib had been ceased and not restarted, and a causative role was considered a reasonable possibility by the investigator.

In Study BRF113929 (BREAK-MB), any Grade increases in creatinine were seen in 7/165 (4%) subjects, and 2 subjects experienced events of ARF (one subject Grade 1 and the other Grade 2). Both episodes resolved and did not require permanent discontinuation of dabrafenib. Neither case was considered related to dabrafenib use by the investigator, although in one case a possible association was considered by this evaluator.

In Study BRF114144, a Subject developed nephritis and renal insufficiency in the setting of cholecystitis that was considered attributable to dabrafenib and lead to treatment discontinuation.

Comment: Although not a frequent occurrence, an effect of dabrafenib on renal function cannot be excluded. This needs to be considered in addition to the potential renal effects as a result of pyrexia accompanied by dehydration, hypotension and acute renal insufficiency.

8.5.3. Other clinical chemistry

8.5.3.1. Pivotal study BREAK-3 and ISS

In Study BRF113683 (BREAK-3), greater variations in glucose levels were observed in the dabrafenib arm than in the DTIC arm, with 93/187 subjects (50%) experiencing hyperglycaemia compared to 25/59 subjects (43%) respectively. 12 subjects (6%) experienced Grade 3 hyperglycaemia in the dabrafenib arm compared to none in the DTIC arm. Meanwhile, 11 subjects (6%) experienced hypoglycaemia in the dabrafenib arm compared to 1 subject (2%) in the DTIC arm.

More subjects in the dabrafenib arm experienced hypernatremia (10 subjects (5%) compared to 1 subject (2%) in the DTIC arm); hyponatremia (14 subjects (8%) compared to 2 subjects (3%) in the DTIC arm); and hypophosphatemia (68 subjects (37%) compared to 8 subjects (14%) in the DTIC arm).

A similar pattern was observed in the integrated safety population, where in particular hyperglycaemia was observed in 240/578 (48%) subjects, and hypophosphataemia in 35% (Table 13).

Table 13. Summary of worst-case chemistry grade changes from baseline grade in BREAK-3 (safety population) and across dabrafenib studies (ISS safety population)

Parameter	BREAK-3								Total Dabrafenib Monotherapy, n (%) (N=578)			
	DTIC, n (%) (N=59)				Dabrafenib, n (%) (N=187)							
	n[a]	Any Grade Increase	Increase to Grade 3	Increase to Grade 4	n[a]	Any Grade Increase	Increase to Grade 3	Increase to Grade 4	n[a]	Any Grade Increase	Increase to Grade 3	Increase to Grade 4
Hypoglycemia	58	1 (2)	0	0	185	11 (6)	0	0	566	49 (9)	0	0
Hyperglycemia	58	25 (43)	0	0	185	93 (50)	12 (6)	0	566	270 (48)	25 (4)	1 (<1)
Hyponatremia	58	2 (3)	0	0	185	14 (8)	4 (2)	0	567	78 (14)	14 (2)	1 (<1)
Hypernatremia	58	1 (2)	0	0	185	10 (5)	0	0	567	22 (4)	0	0
Hypokalemia	58	1 (2)	1 (2)	0	186	4 (2)	2 (1)	0	566	45 (8)	9 (2)	1 (<1)
Hyperkalemia	58	4 (7)	1 (2)	0	186	9 (5)	1 (<1)	0	566	26 (5)	2 (<1)	0
Hypophosphatemia	58	8 (14)	1 (2)	0	186	68 (37)	10 (5)	1 (<1)	565	197 (35)	31 (5)	1 (<1)
Increased creatinine	58	3 (5)	0	0	186	9 (5)	0	0	568	35 (6)	0	1 (<1)
Increased alkaline phosphatase	58	8 (14)	1 (2)	0	185	35 (19)	0	0	567	125 (22)	7 (1)	0
Increased ALT	58	13 (22)	0	0	186	21 (11)	2 (1)	0	567	88 (16)	4 (<1)	0
Increased AST	58	6 (10)	0	0	185	15 (8)	1 (<1)	0	567	73 (13)	2 (<1)	0
Hyperbilirubinemia	58	1 (2)	0	0	185	3 (2)	0	0	565	13 (2)	0	0

Data Source: ISS Table 8.3101

ALT = alanine aminotrasferase, AST = aspartate aminotransferase, DTIC = dacarbazine

a. Number of subjects with an on-therapy lab value

Note: Subjects with missing baseline grade, including those with tests that were not performed at baseline, were assumed to have a baseline grade of 0.

Comment: In the BREAK-3 study, treatment with dabrafenib appeared to impact on clinical chemistry parameters to a greater extent than DTIC, in particular, there were relatively large impacts on glucose and phosphate levels. This observation was supported by the ISS, where it was noted that hypophosphatemia has been observed at a similar frequency and severity with the use of other BRAF inhibitors[16], and thus there may be a class effect for which the mechanism remains unknown. Therefore, monitoring of laboratory markers may be warranted during dabrafenib therapy, and there may be specific implications for use in diabetic patients. This issue was not addressed in the BREAK-3 study or ISS.

8.5.3.2. Other studies

Study BRF113710 (BREAK-2) had similar findings to the pivotal study, with hyperglycaemia observed in 42/90 subjects (47%); hypoglycaemia in 9/90 (10%); hyponatraemia in 14/91 (15%); and hypophosphatemia in 33/91 (36%).

In Study BRF113929 (BREAK-MB), any Grade hyperglycaemia was seen in 70/165 (42%); hypoglycaemia was seen in 23/165 (14%); hyponatraemia was seen in 19/165 (12%); and hypophosphataemia was seen in 48/165 (29%).

In the dabrafenib monotherapy arm of Part C in Study BRF113220, hyperglycaemia was observed in 24/53 (45%) subjects; hypoglycaemia in 0%; hyponatraemia in 10/53 (19%); and hypophosphataemia in 18/50 (36%). There was one case of Grade 4 hypermagnesaemia, and 3 cases (6%) of Grade 3 hypokalaemia.

Comment: The results from the supportive studies support the findings from the pivotal study above.

8.5.4. Haematology

8.5.4.1. Pivotal study BREAK-3 and ISS

In the pivotal study BRF113683 (BREAK-3), haematology abnormalities were observed more frequently in the DTIC arm than the dabrafenib arm. In particular, shifts from baseline to Grade 3 and Grade 4 levels of neutropenia, thrombocytopenia, and leukopaenia were more common in

[16] Zelboraf Medical Review. US Food and Drug Administration website. Available at: <http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202429Orig1s000MedR.pdf>.

the DTIC arm. Grade 3 and Grade 4 abnormalities were uncommon on the dabrafenib arm. Despite this, haematology abnormalities were still observed in the dabrafenib arm with anaemia observed in 39/187 subjects (21%); lymphopenia observed in 31/187 subjects (17%), with 6 (3%) of the latter cases being Grade 3; and neutropenia observed in 11/187 subjects (6%).

Comment: Despite occurring less frequently than with DTIC, haematological abnormalities including anaemia, lymphopenia and neutropenia would still seem important associations with dabrafenib use that warrant monitoring.

In the integrated safety population, the rates of haematological abnormalities were slightly higher than in the BREAK-3 study, with anaemia seen in 135/578 (29%) subjects, lymphocytopenia in 20% with 6% Grade 3 and 5 subjects (<1%) Grade 4, and neutropenia observed in 11%.

Comment: The higher rates of haematological abnormalities observed in the integrated safety population compared to the pivotal BREAK-3 study could be explained by more subjects in the integrated population having had previous anticancer therapies and more advanced disease than in the pivotal study in which all subjects were treatment naive. However, in clinical practice, subjects are likely to have had multiple therapies, and thus the higher rate of haematological abnormalities could be expected. It is noted that although uncommon, higher grade (Grade 3 or 4) abnormalities did occur at a rate of up to 6%, and monitoring for these during treatment may be warranted.

8.5.4.2. Other studies

In Study BRF113710 (BREAK-2), anaemia was observed in 26/91 subjects (29%, of which 7% was Grade 3); lymphopenia observed in 18/91 subjects (20%), and neutropenia 19/91 subjects (21%).

In Study BRF113929 (BREAK-MB), anaemia was observed in 60/165 subjects (36%, of which 2% were Grade 3), lymphopaenia was observed in 37/165 subjects (22%, of which 5% was Grade 3), and neutropaenia was seen in 14/165 subjects (8%, of which 2% was Grade 4).

In the dabrafenib monotherapy arm of Part C in Study BRF113220, anaemia was observed in 12/53 (23%) subjects, lymphopaenia in 16 (30%, of which 4% were Grade 3), and neutropenia in 4 (8%).

Comment: The results of the supportive studies support that of the pivotal study.

8.5.5. Electrocardiograph

8.5.5.1. Pivotal study BREAK-3 and ISS

In Study BRF113683 (BREAK-3), ECG monitoring was performed at baseline, Weeks 3, 6 and 12, and then at 9 weekly intervals thereafter during study treatment. 32/159 (20%) of subjects in the dabrafenib arm experienced any grade increase in QTcB while on study treatment, compared to 7/43 (16%) in the DTIC arm. Although neither arm had any subjects with a QTcB value greater than 500 msec, it was noted that 3/187 subjects (2%) in the dabrafenib arm and 1/59 subject (3%) in the DTIC arm experienced an increase in QTc from baseline of >60 msec.

In the integrated safety population, 90/424 (21%) subjects experienced any increase in QTcB from baseline, and the proportion of subjects who experienced an increase in QTcB of 31 to 60 ms or >60 ms were 16% and 3%, respectively. Increases to >480 ms occurred in 2% of subjects, and no subjects experienced a QTcB of >500 ms while on study treatment.

Comment: Although not definitive, it appears there may be some association between dabrafenib use and QT prolongation. The proportion of patients experiencing any grade increases QT interval in both arms of the BREAK-3 study was similar

(approx 20%), and it is noted that ECG abnormalities are listed as an adverse reaction in the dacarbazine (DTIC) PI. The lack of information on actual QT increases including uncorrected results from the pivotal study limits further analysis.

This finding is consistent with the findings of other BRAF inhibitors (vemurafenib), for which exposure-dependent QT prolongation was observed in studies, and QT prolongation is included as a specific precaution in the vemurafenib PI. Therefore, the association between dabrafenib use and QT prolongation warrants further investigation, and ECG monitoring should occur with dabrafenib use with appropriate precautionary measures taken in the event of its occurrence.

8.5.5.2. Other studies

In Study BRF112680, a dedicated exposure-QTc analysis was performed to determine the relationship between QTc interval and plasma concentrations of dabrafenib and its metabolites for 108 subjects. This revealed that although there was no statistically significant relationship between dabrafenib and QTc, there appeared to be a positive relationship between all three dabrafenib metabolites and QTc. Based on the geometric mean Cmax values observed at the recommended dose of 150 mg BID or the highest dose administered (300 mg BID), the median change in QTcP was predicted to be ≤5.5 msec. At the highest Cmax value observed with any of the metabolites included in the dataset, the median increase was predicted to be ≤18.9 msec. The Sponsor concluded from this analysis that these results represented a low risk of QT prolongation and an acceptable safety profile.

Comment: This exposure-QTc response analysis in Study BRF112680 found that although dabrafenib itself did not significantly impact the QT interval, all three dabrafenib metabolites (hydroxy- carboxy- and desmethyl-dabrafenib) were found to significantly prolong QTc with increasing effect at higher concentrations. Although it is accepted that this effect of the metabolites appeared to be low in this study, it is noted that gelatine capsules with lower bioavailability were used. The proposed dosage and formulation of dabrafenib as 150mg BID in HPMC capsules is predicted to result in concentrations of dabrafenib and its metabolites that are higher than that observed at the maximum dose investigated in Study BRF112680 (300mg BID, gelatine capsules) (see Section 4.2.2.2.3). In light of this, the opinion of this evaluator is that the results of this study do not adequately cover the range of dabrafenib and metabolite concentrations that may occur in clinical practice. Due to the finding that the effect of dabrafenib metabolites on QT interval increases with increasing concentration, these results do not adequately quantify the risk of QT prolongation at the dose and formulation proposed for registration. Therefore, a more thorough QT study may be warranted using the proposed dosage and formulation.

In this same study (BRF112680), 1 subject was identified who mistakenly took 300 mg TID dabrafenib from Study Day 1 to Study Day 48. Although no AEs were reported during this time, the subject was noted to have a mean QTcF of 505 msec on Study Day 8, which resolved and with no further episodes during study participation.

In Study BRF113710 (BREAK-2), the results supported the findings of the pivotal study, with 21/92 subjects (23%) reported to have and abnormal ECG during the study. 20/87 subjects (23%) were recorded to have an increase in QTcB of >31 msec from baseline, and of these, 2 subjects (2%) had an increase of >60 msec. No subjects were recorded to have a QTcB greater than 500 msec while on study treatment.

In Study BRF113929 (BREAK-MB), 25/149 subjects (17%) had any Grade increase in QTcB during the study period, although there were no observations of QTcB>500msec. 6/140 (4%) subjects experienced a >60msec increase from baseline QTc value.

In the dabrafenib monotherapy arm of Part C in Study BRF113220, 7/53 (13%) subjects had any grade increase in QTcF, one of which (2%) had an absolute QTcF value ≥501 msec (although there were no QTcB increases to >481 msec), and two additional subjects (4%) had QTcB increases of >60 msec from baseline (one of which also had had a QTcF increase of >60 msec). None of the abnormal ECG values were considered clinically significant.

Comment: The ECG findings in the supportive studies support the findings of the pivotal study.

8.5.6. Vital signs

8.5.6.1. Pivotal study BREAK-3 and ISS

The CSR reported that no notable changes in vital signs (including blood pressure, heart rate, respiration rate, and basal temperature excluding pyrexia episodes) were identified in the randomised or crossover phases of Study BRF113683 (BREAK-3). However, there did appear to be slight decreases in diastolic (2-3 mmHg) and systolic (4-10 mmHg) blood pressure measurements from baseline in the dabrafenib arm which increased over time, the clinical significance of which was not determined. Changes in temperature (pyrexia) have been discussed in Section 8.4.2.1.1.

No additional issues regarding vital signs were identified in the integrated safety population.

8.5.6.2. Other studies

No notable changes in vital signs (including blood pressure, heart rate, respiration rate, and basal temperature) were identified in Study BRF113710 (BREAK-2).

8.6. Post-marketing experience

Not applicable.

8.7. Safety issues with the potential for major regulatory impact

8.7.1. Liver toxicity

The potential for liver toxicity cannot be excluded, but would appear to be low as discussed in Section 8.5.1.

8.7.2. Haematological toxicity

There is a moderate risk of haematological toxicity, as discussed in Section 8.5.4, however, this is not unacceptable in light of dabrafenib's proposed indication as an anticancer agent.

8.7.3. Serious skin reactions

Apart from a single episode of moderate phlyctena on the limbs in ongoing Study BRF113928 (see Section 8.4.2.1.2), there were no other reports of serious skin reactions in association with dabrafenib use. As noted in Section 8.4.2.1.1, low grade PPE was observed with moderate frequency.

8.7.4. Cardiovascular safety

An association between dabrafenib use and reductions in LVEF, cardiac valvular abnormalities, and QTc prolongation cannot be excluded, as is discussed in Section 8.4.2.1.1.

8.7.5. Unwanted immunological events

As described in Section 8.4.2.1.2, in ongoing Study BRF113928 there was one isolated reported SAE of clinically significant moderate phlyctena on the limbs immediately following administration of dabrafenib, which was repeated on rechallenge. This reaction was thought to be related to dabrafenib. No other similar reports have been made, and the significance of this remains uncertain.

8.8. Other safety issues

8.8.1. Safety in special populations

The integrated safety population was analysed according to the following subgroups:

- Age: <65 years (N=453); ≥65 years (N=125)

  Although the total proportion of subjects who experienced AEs were similar amongst both groups (98% vs. 95% for those aged ≥65 and <65 respectively), subjects aged ≥65 years had a greater proportion who experienced SAEs compared to those aged <65 (41% vs. 22%), and greater proportion of AEs and SAEs considered related to study treatments (95% vs. 84% and 26% vs. 14% respectively). In addition, there were a higher proportion of subjects who had AEs leading to dose reduction or dose interruption/delay in those aged ≥65 years. AEs reported more frequently in those aged ≥65 years included hyperkeratosis, fatigue, skin papilloma, chills, constipation, seborrheic keratosis, peripheral oedema, actinic keratosis, decreased weight, and dyspnoea. AEs reported more frequently in those aged >65 years included alopecia and PPE syndrome.

Comment: Increased frequency of SAEs in older age groups is not unexpected.

- Gender: Male (N=352); Female (N=226)

  There were no significant differences in the absolute rates of AEs and SAEs, or those considered related to study treatment between subject genders. In addition, there proportion of AEs leading to dose reduction or dose interruption/delay was similar between the two groups.

- Presence of active brain metastases prior to initiation of dabrafenib monotherapy: No (N=393); Yes (N=185)

  The incidence of AEs and AEs related to study treatment were lower in subjects with active brain metastases compared with those without (92% vs. 97% and 83% vs. 88%, respectively). The proportion of those with AEs leading to dose modifications was similar between the two groups. More subjects with active brain metastases experienced an SAE in comparison to subjects without (29% vs.24%). In particular, events of intracranial/cerebral haemorrhage were higher in the brain metastases subgroup.

- It was noted that the effect of race on the safety of dabrafenib was not assessed as subjects were predominantly White (>95%) in keeping with the epidemiology of patients with metastatic melanoma.

8.8.2. Safety related to drug-drug interactions and other interactions

Dabrafenib has been found to be a moderate to potent cytochrome P450 (CYP) 3A4 inducer, and induces CYP3A4-mediated metabolism. Therefore, co-administration of dabrafenib and medications which are affected by the induction of these enzymes may result in loss of efficacy. The Sponsor recommended that if co-administration of these medications is necessary, investigators should monitor subjects for loss of efficacy or consider substitutions for these medications.

Dabrafenib metabolism is mediated by CYP2C8 and CYP3A4, and both hydroxy- and desmethyl-dabrafenib are CYP3A4 substrates. Based on interim data, modest increases (48-61%) in repeat-dose AUC(0-τ) of dabrafenib, hydroxydabrafenib, and desmethyl-dabrafenib were noted with repeat-dose ketoconazole. Therefore, the Sponsor cautioned that drugs that are strong inhibitors or inducers of CYP3A4 and CYP2C8 may increase or decrease dabrafenib exposure and should be used with caution.

Comment: The recommendations of the sponsor would seem reasonable.

8.8.3. Dabrafenib capsule shell type

In early clinical studies, dabrafenib study drug was provided in gelatine capsules. In the pivotal study BREAK-3 and the supportive Phase II study BREAK-MB, the gelatine capsules were replaced with dabrafenib in hydroxypropyl methylcellulose (HPMC) capsules, which provided better stability and enhanced shelf-life for dabrafenib clinical supplies. In Study BRF113468 (food effect/particle size), exposure to dabrafenib was higher in subjects receiving HPMC capsules as compared with gelatine after single-dose administration. (See Section 3.2 for further discussion).

In the ISS, safety results were summarised according to the type of capsule shell received: gelatine (n=139) or HPMC (n=387). Overall, the incidence of AEs (96% vs. 95%), SAEs (28% vs. 26%), and AEs leading to dose modifications were similar in subjects receiving gelatine or HPMC capsules. Fatal SAEs were seen only in HPMC-treated subjects (5 cases (1%) compared to none in the gelatine subgroup). This was not considered in the ISS to be related to capsule shell type, as all 5 deaths were attributable to underlying disease. Rates of pyrexia (27% vs. 29%) and SCC (5% vs. 6%) were similar in HPMC and gelatine subgroups. Rates of other AEs varied to differing degrees between the two groups, but did not appear to favour one group over the other of follow any particular pattern.

Comment: From the PK analysis, it might be expected that the rates of AEs would be greater with the use of HPMC capsules due to achieving greater dabrafenib exposures. This was not observed in the subgroup analysis. It is noted that the number of subjects treated with HPMC is greater than that treated with gelatine capsules, and the latter are no longer being used in trials. Therefore, the impact of the use of gelatine capsules on the overall safety profile could be considered small.

8.8.4. Use in pregnancy and lactation

No data exists on the use of dabrafenib in pregnant or lactating women. Animal studies showed reproductive toxicity, including teratogenicity and testicular toxicity in male animals without clear evidence of reversibility.

Therefore, the Sponsor recommended that dabrafenib should not be used during pregnancy, and women of childbearing potential should be advised to use adequate contraception and avoid becoming pregnant while receiving treatment with dabrafenib. Due to the potential decrease in exposure due to CYP3A4 induction, oral contraceptives are not considered adequate and an alternate method of contraception should be considered. The safe use of dabrafenib during lactation has not been established. It is not known whether dabrafenib is excreted in human milk, and the Sponsor recommended that breast feeding should be discontinued during treatment with dabrafenib.

Comment: The recommendations of the Sponsor would seem reasonable.

8.8.5. Overdose

There is no known antidote for dabrafenib. Dabrafenib has been studied at doses up to 300 mg BID (FTIH Study BRF112680). In subsequent studies, a study drug overdose was defined as the administration of >300 mg dabrafenib as a single dose or >600 mg daily. In the 578 subjects included in the integrated dabrafenib safety population, 1 subject was identified who received

repeat doses of dabrafenib monotherapy higher than 600 mg daily. This subject in Study BRF112680 mistakenly took 300 mg TID dabrafenib from Study Day 1 to Study Day 48 and reported no AEs during this time, although was noted to have a mean QTcF of 505 msec on Study Day 8, which resolved and with no further episodes during study participation. Correct dosing of 100 mg TID was instigated on Study Day 49, and dabrafenib was continued until Study Day 153 when it was discontinued due to disease progression.

The safety of dabrafenib at doses higher than 150mg BID was assessed in the FTIH study BRF112680, where 10 subjects were assigned to a dose of dabrafenib (gelatine capsules) of 300 mg BID. The mean duration of treatment in this cohort was 180.5 days, and the maximum treatment duration was 295 days. Common AEs observed in this cohort were headache (50%), fatigue (40%), pyrexia (40%), pain in extremity (40%), rash (40%), arthralgia (40%), and cough (40%). The steady-state exposure to dabrafenib following repeat dosing of 300 mg BID (gelatine capsules) was not observed to be different from exposure following repeat dosing of 150 mg BID (HPMC capsules). A clinical benefit for doses of dabrafenib higher than the proposed 150 mg BID HPMC capsules has not been established.

8.8.6. Serious adverse events from dabrafenib monotherapy clinical studies following data cut-off

A summary of SAEs from all dabrafenib studies included in the ISS (BREAK-3, BREAK-2, BREAK-MB, BRF113220 (dabrafenib and trametinib), and BRF112680 (FTIH)) in addition to studies BRF113771 (repeat dose PK and drug interaction study), BRF115252 (compassionate care – line listing of SAEs provided, but no CSR or study synopsis included in submission), BRF113928 (non-small cell lung cancer) and BRF114144 (rollover) through to 30 March 2012 was provided.

Comment: Insufficient detail was provided on the number of subjects and duration of treatment during this period to make an informed evaluation of these SAEs, however the reported findings are summarised here.

Of approximately 291 subjects included in the ISS, following data cur-off until 30 march 2012 there were an additional 4 cases of fatal SAEs reported, 3 of which were not considered to be related to dabrafenib treatment, and the other subject was a 78 year old make with cardiac risk factors who died from myocardial infarction and acute coronary syndrome. 56 subjects experienced 97 SAEs, of which there were 31 neoplasms (including benign, malignant and unspecified: 29 of which were SCC of the skin, Bowen's disease or keratoacanthoma), and 8 cases of pyrexia.

From the other four studies (BRF113771, BRF115252, BRF113928 and BRF114144), a summary of SAEs was not provided, but 3 significant events were reported, two of which have already been discussed in this CER (episodes of blisters in a subjects from Study BRF113928, and nephritis and renal insufficiency in Study BRF114144). In addition, there was an episode of pancreatitis in Study BRF115252 which led to discontinuation of dabrafenib.

8.9. Evaluator's overall conclusions on clinical safety

Dabrafenib has an adverse event profile that is distinct from the cytotoxic chemotherapy regimens. Overall 96% of subjects in the integrated safety population experienced an AE, and 26% of subjects reported a SAE. 24% subjects died in the integrated safety population, and disease under study reported as the primary cause of death in 97%.

Overall, dabrafenib was well tolerated and appeared to have a manageable safety profile. In the integrated safety population, only 2% of subjects discontinued treatment due to adverse effects, and 14% of subjects had a dose reduction due to adverse effects.

In particular, the following AEs were found to be clinically relevant to dabrafenib's use:

- **Premalignant and malignant skin lesions:** Dabrafenib has been found to increase the risk of premalignant and malignant skin lesions, with a rate of 9% in the integrated safety population. This is in keeping with the results from vemurafenib studies, and therefore is likely to be a class-effect of BRAF inhibitors. Cases of cutaneous SCC reported in the BREAK-3 study were detected early with regular dermatologic screening, and the cumulative incidence in the integrated safety population appears to plateau. Therefore, early and frequent dermatologic monitoring is warranted with dabrafenib use. However, the long term effects of dabrafenib on the rate and severity/aggressiveness of cutaneous malignancies are not known in light of limited follow-up duration, and the continued monitoring and reporting of these events would be of benefit. The current data does not suggest an association between use of dabrafenib and the development of other malignancies (other than SCC or keratoacanthoma), including no increased risk of new primary melanoma above what is expected in the melanoma patient population.
- **Pyrexia:** The study results suggest dabrafenib treatment is associated with pyrexia, with a frequency of 27% in the integrated safety population. The mechanism of pyrexia remains unknown, and 50% of cases occurred within 2 weeks of starting treatment. This pyrexia has the potential to be severe, with 18% of cases in the integrated safety population being considered SAEs, and this can have significant impacts on other organ systems and overall functioning. It is noted that pyrexia is not listed as an adverse effect of the currently registered BRAF inhibitor vemurafenib.
- **Cardiovascular adverse events:** Monitoring of cardiovascular AEs was performed based on AEs observed with other kinase inhibitors, and following the results of preclinical studies with dabrafenib. Dabrafenib was associated with a decrease in LVEF from baseline in 54% of subjects in the BREAK-3 study, similar to that for DTIC, however the magnitude of the decrease appeared to be slightly greater with dabrafenib. Cardiac valvular abnormalities were observed in preclinical studies of dabrafenib, and were observed in 2% of subjects in the BREAK-3 study and considered possibly related to study treatment. Due to the rare occurrence of these events and the limited period of follow up to date, an association between dabrafenib use and the cardiovascular adverse events of decreased LVEF and cardiac valvular abnormalities cannot be excluded, and further monitoring and follow up as part of the Risk Management Plan are warranted. It is noted that these conclusions are at odds with those drawn by the Sponsor as outlined in the clinical summaries.
- **QT prolongation:** There may be some association between dabrafenib use and QT prolongation, with 21% of subjects in the integrated safety population experiencing any increase in QTcB from baseline. In Study BRF112680, an exposure-QTc analysis found no statistically significant relationship between dabrafenib and QTc, however there was a positive relationship between all three dabrafenib metabolites and QTc, with the median change in QTcP predicted to be ≤5.5 msec at the highest doses tested. Although this was assessed by the Sponsor as indicating low risk of QT prolongation, due to the greater bioavailability of dabrafenib as HPMC capsules compared to the gelatine capsules used in this study, a clinically relevant effect of dabrafenib metabolites on QT prolongation cannot be excluded. As QT prolongation is also listed as an adverse effect of the BRAF inhibitor vemurafenib, for which exposure-dependent QT prolongation was observed in studies, a more thorough QT study may be warranted using the proposed dosage and formulation for registration. ECG monitoring should occur with dabrafenib use with appropriate precautionary measures taken in the event of its occurrence.
- **Palmar-Plantar Erythrodysesthesia (PPE):** This was observed in 20% of subjects in the dabrafenib arm of the BREAK-3 study, and in 13% of the integrated safety population. Most cases were of low grade.
- **Cerebral haemorrhage in brain metastases:** Three deaths were attributed to the SAE of cerebral haemorrhage in the BREAK-MB study. In at least one of these subjects, bleeding

may have been precipitated by tumour shrinkage as a result of dabrafenib use. Therefore, bleeding into responding CNS lesions may be an AE of dabrafenib in the setting of brain metastases which needs to be monitored.

Other general conclusions drawn from the safety data include:

- The [risk of an] association between dabrafenib and hepatocellular injury appears to be low, but cannot definitively be excluded. Ongoing hepatic monitoring may be warranted with long-term use.
- Although not a frequent occurrence, an effect of dabrafenib on renal function cannot be excluded, and renal monitoring with long-term use may be warranted. In particular, the risk of renal failure may be exacerbated by the presence of drug-induced pyrexia with secondary renal insufficiency.
- There appears to be an association with dabrafenib and hyperglycaemia (observed in 48% of subjects in the integrated safety population), and hypophosphataemia (observed in 35%). Therefore, monitoring of laboratory markers may be warranted during dabrafenib therapy, and there may be specific implications for use in diabetic patients.
- Despite occurring less frequently than with DTIC, haematological abnormalities would still seem important associations with dabrafenib use. In the integrated safety population, anaemia was seen in 29% subjects, lymphocytopenia in 20% (with 6% Grade 3 and 5 subjects (<1%) Grade 4), and neutropenia observed in 11%. The frequency may be increased when used with other therapies. Therefore, monitoring for haematological abnormalities may still warrant monitoring.

It is noted that arthralgia and rash were commonly reported as low grade AEs across all studies with a frequency of around 30%. This did not appear to have been investigated further within the submission as to possible mechanisms (e.g. possible autoimmune cause).

8.9.1. Comparison of dabrafenib's safety profile with that of the anti-melanoma agents vemurafenib and ipilimumab:

As discussed, the absence of head-to-head trails between dabrafenib and the now first-line agent vemurafenib and the second-line agent ipilimumab in the treatment of advanced or metastatic melanoma, mean that direct comparisons of their safety profiles cannot be made.

On examination of the product information for vemurafenib, there appear to be BRAF inhibitor class effects that are shared with dabrafenib, specifically an increase in cutaneous skin cancers, ophthalmic reactions and potentially QT prolongation. This latter finding strengthens the need for further studies into the effect of dabrafenib on the QT interval in light of study results suggesting an association. Liver laboratory abnormalities are also listed as an adverse effect of vemurafenib, and this may also be associated with dabrafenib use. It is noted that there appears to be a decreased incidence of hypersensitivity, dermatologic and photosensitivity reactions with dabrafenib compared to vemurafenib, however a higher incidence of pyrexia, PPE and possibly cardiac valvular abnormalities that need to be monitored. No information was provided in the vemurafenib PI regarding potential adverse effects in the setting of brain metastases.

On examination of the PI for ipilimumab, the main adverse events listed are those associated with inflammatory adverse reactions resulting from increased or excessive immune activity. These include serious immune-mediated gastrointestinal events, hepatotoxicity, skin toxicity, neurological events, and endocrinopathy. Therefore, the adverse event profile of ipilimumab is considerably different to that of dabrafenib, in keeping with their differing mechanisms of action. Comparison of the relative severity of the adverse event profile of these two agents was not performed, given the absence of head-to-head data.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of dabrafenib in the proposed usage are:

- Clinically relevant improvement in PFS was found in the BREAK-3 study for subjects with BRAF V600E mutation-positive advanced or metastatic melanoma, excluding brain metastases. Compared to standard therapy with DTIC, treatment with dabrafenib 150mg BID (HPMC capsules) resulted in an adjusted hazard ratio for PFS of 0.30 (95% CI: 0.18-0.51; p<0.0001). These results were supported by the secondary outcomes of BREAK-3 and also the BREAK-2 study, and some improvement in Quality of Life measures was also observed. These benefits can be considered highly significant in light of the traditional poor prognosis of patients with metastatic melanoma disease.
- Although it would seem efficacious, due to the absence of a Phase III trial, it cannot definitively be concluded that dabrafenib is superior to currently used local therapies (surgery or SRS) in the management of BRAF V600E positive metastatic melanoma CNS lesions (which includes up to 70% of patients with metastatic melanoma).
- Evidence for the efficacy of dabrafenib in patients with BRAF V600K mutation positive metastatic melanoma is not convincing, and the clinical significance in this patient population remains undetermined. Particularly with respect to patients with BRAF V600K metastatic melanoma to the brain, there is no evidence of superiority of dabrafenib compared to appropriate local management (surgery o SRS).

9.2. First round assessment of risks

Overall, the risks of dabrafenib in the proposed usage generally appear to be manageable. These include:

- There is an increased risk of premalignant and malignant skin lesions (9%), which are managed adequately by early detection with regular dermatologic screening. However, the long term effects of dabrafenib on the rate and severity/aggressiveness of cutaneous malignancies are unknown.
- Dabrafenib treatment is associated with an increased risk of pyrexia (27%) which commonly occurs within 2 weeks of starting treatment. Pyrexia has the potential to be severe (18% of cases), which can have subsequently impact on other organ systems, although generally does not require discontinuation of treatment.
- An association between dabrafenib use and LVEH, cardiac valvular abnormalities and QTc prolongation cannot be excluded.
- Low grade Palmar-Plantar Erythrodysesthesia is associated with dabrafenib use.
- There is the potential serious risk of cerebral bleeding into responding CNS lesions with brain metastases. This risk may be greater when dabrafenib is used in conjunction with other therapies.
- There appears to be an association between use of dabrafenib and hyperglycaemia (observed in 48%) and hypophosphotaemia (observed in 35%).
- Haematological abnormalities are associated with dabrafenib use, although at rates lower than other cytotoxic chemotherapeutic agents.

- An association between the use of dabrafenib and small increases in hepatocellular and renal insufficiency cannot be excluded. Risk of renal failure may be increased in the setting of pyrexia.
- The PK of dabrafenib in ethnic groups other than Caucasians has not been studied and remains unknown. As these groups may have differing enzyme activity, due to a large proportion of dabrafenib being cleared by metabolism, there is risk of overexposure.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of dabrafenib is unfavourable given the proposed usage, but would become favourable if the changes recommended in Section 10 are adopted.

This is because although the balance of risks to benefits is favourable in subjects with BRAF V600E (and most-likely V600K) mutation-positive advanced or metastatic melanoma excluding brain metastases, there issues relating to patients with brain metastases which need to be further addressed by the sponsor. In addition, there are aspects of the PI for which modifications are recommended.

10. First round recommendation regarding authorisation

- It is recommended that dabrafenib be registered for the treatment of BRAF V600E mutation-positive advanced or metastatic melanoma, excluding brain metastases, pending satisfactory address of the clinical questions posed in Section 11.
- It is recommended that more guidance be provided for the use of dabrafenib in the setting of BRAF V600E positive melanoma brain metastases. Specifically guidance is needed as to whether dabrafenib should be given following local management (surgery or SRS) that is deemed appropriate using current criteria which may be more efficacious, or whether other local treatments should be excluded due to the potential increased risk of SAEs. Additional recommendations and justifications are required, which may be result in refining the proposed indication.
- Due to the poor prognosis of metastatic melanoma and, until recently, the lack of an effective treatment, there may be a role for treatment of patients with BRAF V600K metastatic melanoma, provided the limitations in the evidence with regards to this patient subgroup are acknowledged and ongoing data is collected for further assessment. It is recommended that dabrafenib treatment of BRAF V600K metastatic melanoma to the brain should be subject to additional guidance as above.
- The efficacy of dabrafenib for other BRAF V600 mutation types (including V600D, V600G and V600R) have not been investigated, and are therefore undetermined, and therefore it is recommended that they be excluded from the indication.
- The proposed dosage regimen and formulation of dabrafenib 150mg BID in HPMC capsules is acceptable.
- Changes to the PK section of the PI are recommended.

  Additional precautions are recommended for inclusion in the PI, including information on the risk of cardiovascular abnormalities, QT prolongation, cerebral haemorrhage in bran metastases, use in hepatic impairment, and risk of hepatic and renal impairment.[17]

[17] The section describing the evaluator's assessment and recommendations on the PI and other product literature is not included in the Extract.

11. Clinical questions

11.1. Pharmacokinetics

- Is further analysis available from Study BRF113771 to better characterise the dose-proportionality of dabrafenib in HPMC capsules?
- It was reported in the Clinical Pharmacology Summary in Module 2.7.2 of the submission (p41) that the CL/F of dabrafenib after repeat dosing at 150mg BID was measured at 35 L/hr in Study BRF113683 (BREAK-3), although no reference to this could be found in the study CSR. Could the Sponsor please provide the supporting data for this claim?
- Due to extensive metabolism of dabrafenib, is additional information available on the impact of drug interactions and genetic or ethnic variations in metabolism? Are updated results available for the drug interaction study BRF113771?
- Are interim results available for the studies investigating the PK of dabrafenib in subjects with hepatic and renal impairment?

11.2. Efficacy

- Please provide data on the updated OS at 12 months follow-up in Study BRF113710 (BREAK-2) as presented in Table 4 of Module 2.7.3 Summary of Clinical Efficacy (p22), as this could not be found in the study CSR.
- Similarly, are updated OS data available for Study BRF113683 (BREAK-3)?
- The data on the efficacy of dabrafenib in subjects with BRAF V600K mutations is equivocal, and without head-to-head trials, what argument can be made for dabrafenib's superiority over conventional management, particularly in light of the improved outcomes with currently available therapies vemurafenib and ipilimumab?
- What is the justification for including all BRAF V600 mutation types in the indication in the absence of data for mutation types other than V600E and V600K?
- Can more information be provided to justify and specify the proposed use of dabrafenib in the setting of BRAF V600 positive melanoma brain metastases? Specific questions include whether dabrafenib should be used prior to, after, or instead of local management (surgery or SRS) that is deemed appropriate using current criteria. In addition, under what circumstances (e.g. degree of tumour burden) are the different treatments are deemed appropriate? These details may need to be specified under INDICATIONS in the PI.
- Are there any studies (clinical or pre-clinical) or analyses currently in progress to assess the efficacy and safety of dabrafenib compared to now currently available newer treatments for advanced or metastatic melanoma, including the BRAF inhibitor vemurafenib or the monoclonal antibody ipilimumab? If so, when will results be available? If not, what is the justification for omission of these comparisons in light of the current availability of these agents?

11.3. Safety

- Are additional precautions or monitoring required in the setting of brain metastases to mitigate the potential effect of bleeding into CNS lesions? Are recommendations needed as to the use of other local therapies in the treatment of patients with brain metastases?
- Given the limitations of the exposure-QT analysis in Study BRF112680 (discussed in Section 8.5.5.1.2), is a more thorough QT study in progress or planned using the proposed dosage

and formulation (150mg BID, HPMC capsules)? What is the justification if not, given that the effect on QT interval will not have thoroughly been investigated at the proposed dosage and formulation when dabrafenib metabolites have a known effect on QT prolongation? Furthermore, is more information available from the pivotal BREAK-3 study on QT prolongation, including analysis of central tendency: actual increase (mean and median), and uncorrected values and Fridericia's correction?

- Please provide data from Study BRF113683 (BREAK-3) to support the claim of an incidence of phototoxicity of 3% in the dabrafenib arm, as stated in the conclusions of the CSR.

11.3.1. Other

- Please provide an update on progress on the commercial availability of a diagnostic test for detection of BRAF V600E and V600K mutation types.

12. Second round evaluation of clinical data submitted in response to questions

Note: The sponsor's responses to the above questions were assessed by the Delegate in the Overview for this application (see AusPAR section on *Overall conclusion and risk-benefit assessment*).

13. References

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14. Appendix 1. Population PK of dabrafenib in subjects with solid tumours:

14.1. Summary

14.1.1. Objectives

The objectives of this study were to: 1) establish and evaluate the predictive population PK model that describes the PK of dabrafenib in subjects with solid tumours, including estimation of population parameters, inter-individual variability of model parameters, and intra-individual variability of dabrafenib concentrations; 2) evaluate the effect of various demographic factors/potential covariates on dabrafenib PK; 3) provide post-hoc estimates of the individual PK parameters for a subsequent PK/PD evaluation.

14.1.2. Methodology

Design: Dabrafenib concentration-time, dosing, demographics and covariate data from the FTIH Study (BRF112680, Part 1 and Part 2), Phase II studies (BRF113710 [Section 7.1.2.1] and BRF113929 [Section 7.1.2.2]), and Phase III study (BRF113683 [Section 7.1.1.1]) were used in the analysis, as detailed in the table below.

Table 14. Studies included in the population PK analysis

Study No.	Study Description	Dose and Administration	PK Assessments
BRF112680	Phase I, Open-Label, Multiple-Dose, Dose-Escalation, FTIH study of the BRAF Inhibitor GSK2118436 in Subjects with Solid Tumors. Study was conducted in 2 parts: Part 1: Single and Repeat Dose Escalation to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics and identify the recommended Phase 2 dose (RP2D) using accelerated dose titration; 3+3 dose escalation and PKPD expansion; Part 2: Cohort Expansion in Subjects with V600 Mutation Positive Tumor (melanoma with or without brain metastases, and non-melanoma) to further explore the safety profile, PK and clinical activity of GSK2118436	Part 1: Cohorts 1 to 10 with daily doses ranging from 12 mg (12 mg QD) to 600 mg (300 mg BID). Cohort 1 (12 mg QD), Cohort 2 (35 mg QD), Cohort 3 (35 mg BID), Cohort 4 (70 mg BID), Cohort 5 (100 mg BID), Cohort 6 (100 mg TID), Cohort 7 (150 mg BID), Cohort 8 (200 mg BID), Cohort 9 (200 mg BID), and Cohort 10 (300 mg BID) with 1-20 subjects per cohort. Part 2: Cohort A (V600 mutation-positive melanoma subjects with and without asymptomatic, untreated, brain metastases at 150 mg BID; n=30), Cohort B (V600 mutation-positive solid tumors other than melanoma at 150 mg BID; n=20), Cohort C (V600E mutation-positive melanoma subjects at a lower dose of 50 mg BID; n=20). GSK2118436 was dosed using gelatin capsules	Part 1: Full PK on Day 1 (generally PK samples up to 24 hrs), and/or Day 8 or 15 (PK samples up to 10-12 hrs) Part 2: Sparse sampling (trough only up to Cycle 4)
BRF113710	Phase II, single-arm, open-label study to assess the efficacy, safety, and tolerability of GSK2118436 administered twice daily as a single agent in subjects with BRAF mutant metastatic melanoma.	Dose of 150 mg BID (gelatin capsules)	Predose, and 1-3 post-dose at Week 3 and Predose (morning) or afternoon at Weeks 6, 9, 12, 20 and 28
BRF113683	Phase III, randomized open-label study comparing the efficacy, safety, and tolerability of GSK2118436 to dacarbazine (DTIC), in subjects with BRAF mutant metastatic melanoma. Subjects will be randomized 3:1 to receive GSK2118436 or DTIC	GSK2118436: 150 mg BID (HPMC capsules) DTIC: 1000 mg/m2 Q3 weeks	ALL: Predose (morning) or afternoon at Weeks 3, 6, 9, 12, 18 and 24 SUBSET: Full PK (up to 8 hr post-dose) at Week 6
BRF113929	BRF113929: A Phase II Open-Label, Two-Cohort, Multicentre Study of GSK2118436 as a Single Agent in Treatment Naive and Previously Treated Subjects with BRAF Mutation-Positive Metastatic Melanoma to the Brain	GSK2118436: 150 mg BID (HPMC capsules)	Predose, and 1-3 post-dose at Week 4 and Predose (morning) or afternoon at Weeks 8, 16, 24 and 32.

The population PK model was developed using a non-linear mixed-effect modelling approach; the NONMEM 7.2.0 software with the first order conditional estimation method with interaction (FOCEI) was used. The data from study BRF112680 (complete data of Part 1 and partial data of Part 2) were used to establish the preliminary semi-mechanistic base model. The model was then simplified to make it more feasible for exploration of covariates and to adapt to mostly sparse sampling of the other studies (by simplifying absorption, excluding inter-occasion variability, and substituting the mechanistic enzyme-mediated description of clearance induction by dependence of clearance on time and absorbed dose). Data from all 4 studies was then used to finalise the base model and to establish the covariate model. A full model approach was used to evaluate covariates.

Comment: The sparse sampling methods used in three of the four studies used in this analysis, and therefore the need to exclude inter-occasion variability, is a limitation of this study, and may spuriously inflate the inter-individual variability that is measured.

Entry criteria: In Study BRF112680, the majority of subjects had BRAF V600 mutation positive melanoma or other tumours. Study BRF113710 was a Phase 2 study in subjects with BRAF V600 mutation positive melanoma, Study BRF113929 was a Phase 2 study in subjects with BRAF V600 mutation positive melanoma who had brain metastases, and Study BRF113683 was a Phase 3 study in subjects with BRAF V600 mutation positive melanoma.

Treatments: Study BRF112680 explored a wide range of dabrafenib doses and regimens, while all the other studies used the recommended dose (150mg BID), as detailed in the above table.

In studies BRF112680 and BRF113710, dabrafenib was administered in gelatine capsules, while in studies BRF113929 and BRF113683 the drug was administered in HPMC capsules. Data from the clinical pharmacology study BRF113468 indicated increased exposure of dabrafenib when administered in HPMC capsules relative to gelatine capsules with a LS mean (95% CI) AUC(0-∞) ratio of 1.80 (1.32, 2.46) after single dose administration.

PK sampling and analysis: Of the 4 studies included in this analysis, Study BRF112680 was the only study that employed serial PK sampling and explored a wide range of doses and regimens. All the other studies used the recommended dose and employed sparse sampling, with majority of samples obtained after steady-state has been achieved, as detailed in the table above. A subset of subjects enrolled in the Phase 3 study (BRF113683) had serial PK conducted after repeat dosing. See above table for more details.

This analysis was based on parent concentrations only. Investigation of covariates that may impact exposure to metabolites was presented separately. All plasma PK samples in all studies were analysed for dabrafenib using a validated analytical method based on LLE followed by UHPLC/MS/MS analysis. The LLQ for all analytes was 1 ng/mL using a 50 µL aliquot of human plasma.

Development of the population PK model consisted of building the base model (based on a 2-compartment model) followed by the development of a covariate model.

14.1.3. Study participants

Number of subjects: All subjects with available dosing, actual sampling time and dabrafenib concentration data were included in the datasets and used in the analysis. The final dataset for the analysis (Dataset 2) included 3787 dabrafenib plasma concentrations of 595 subjects as follows: 1931 samples from 181 subjects in study BRF112680, 443 samples of 87 subjects in study BRF113710, 508 samples of 148 subjects in study BRF113929, and 905 samples of 179 subjects in study BRF113683.

569 (95.6%) subjects had BRAF V600 mutation positive melanoma, median age was 54 years (range 20-93 years), median weight was 78 kg (range 36.2 - 149.5kg), 61.0% of the population was male, and 98.5% were White. 233 (39.2%) and 30 (5.0%) subjects had mild and moderate

renal impairment respectively (GFR range of 39.7 to 247.6 mL/min/1.73m2). 65 subjects (10.9%) had mild hepatic impairment (only 3 (0.5%) subjects had moderate hepatic impairment so these were grouped together with subjects with mild impairment). There were no subjects with severe renal or hepatic impairment in the data set. 148 (24.9%) and 92 (15.5%) subjects were taking mild CYP3A4 inhibitors and inducers respectively (8 (1.3%) subjects taking strong CYP3A4 inhibitors were grouped together with users of mild CYP3A4 inhibitors).

Analysed: It was reported that: 'missing concentration values, pre-dose plasma samples, and observations below the limit of quantification were excluded from the analysis. Concentration values with missing or inconsistent sample or dosing times were not included in the analysis. Concentration values – outliers (such as values inconsistent with dosing history, or with subject's PK profile, or values > 500 ng/mL at more than 10 hours post-dose) caused by dosing, timing or other errors were excluded from the analysis. All excluded concentrations (except missing values) were kept in the data sets, but were commented out.' In total, 276 or 6.8% of samples were excluded from the analysis.

Comment: It is noted that there appear to be a large number of observations were excluded from the analysis due to being 'outliers' as defined above. These included a total of 116/3787 (3%) of observations across all studies. No other reasoning was given for the exclusion of these observations, and no sensitivity analysis was performed to assess the impact of their inclusion in the analysis. As the inclusion of these observations in the analysis could conceivably alter the results, this failure to assess the impact of their exclusion can be considered a limitation of this study.

14.1.4. Population PK results

Development of base Population PK Model: The development of the population PK model consisted of building the base model followed by the development of a covariate model. First, the preliminary base population PK model was developed using the data from study BRF112680, as data from this study was available earlier. Base model selection was driven by the data and was based on evaluation of goodness-of-fit plots, successful convergence, plausibility and precision of parameter estimates, and the minimum objective function value. Investigation of covariate-parameter relationships was based on range of covariate values in the dataset (including data on demographics, disease characteristics, laboratory values, and concomitant medications), scientific interest, mechanistic plausibility, and exploratory graphics. Once all studies were completed and final data were available, the base model was updated, including an effect of capsule shell, and covariates that influence PK of dabrafenib were explored to identify the final model. The full model approach was implemented, and the ability of the model to describe the observed data was evaluated graphically and investigated using predictive check procedures and bootstrap analysis, followed by elimination of insignificant or poorly estimated covariates.

The base PK model was a 2-compartment model with first-order absorption (Ka) and elimination and absorption lag time (Tlag). The model included oral volume of distribution of central (Vc/F) and peripheral compartments (Vp/F), distributional clearance (Q/F), relative bioavailability (F), and absorption rate constant (Ka). Elimination was described by combined linear (non-inducible CL_0/F) and enzyme-mediated (inducible CL_{ind}/F) clearance, the latter increasing almost linearly with dose and increasing with time until it reached steady-state, with a half-life of induction of T50. Based on T50 estimate of 67 hrs, steady-state is predicted to be achieved within 14 days of dosing. Inter-individual variability (IIV) was incorporated assuming a log-normal distribution and described by an exponential error model. Inter-occasion variability (IOV) was only used in the initial model.

Following the establishment of the base model, the covariate model was built, and included the covariates listed in the table below. A full model approach was used where all covariate-parameter relationships of interest were entered in the model. Covariates with CIs that included the null value were excluded from the model to arrive at the final covariate model. Continuous covariates were included in the model using a power function, while for categorical covariates, the fractional change in the typical parameter value was determined.

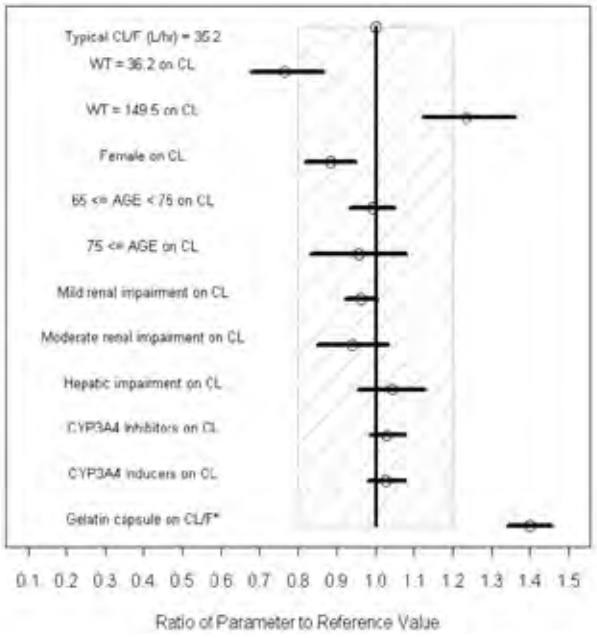
Table 15. Covariates planned to be investigated in the covariate model

Covariate	Model Component	Rationale
Capsule type [a]	F, Ka	A clinical pharmacology study indicated higher bioavailability of HPMC capsules relative to gelatin
Weight	CL/F, Vc/F, Q/F, Vp/F	Body weight influences the model parameters for many drugs.
Gender	CL/F, Vc/F	Evaluation of the gender effect is clinically important.
Age (as continuous covariate and by age group)	CL/F	Evaluation of the age effect is clinically important
Race and ethnicity (if data permit)	CL/F, Vc/F	Evaluation of the race and ethnicity effect is clinically important.
Concomitant CYP2C8, CYP3A4, and PGP inducers and inhibitors grouped as classes	CL_{ind}	GSK2118436 is metabolized through CYP2C8 and CYP3A4, therefore inhibitors/ inducers of this pathway may alter GSK2118436 exposure
Renal impairment (MDRD and categorized levels of impairment)	CL/F	Renal impairment may reduce clearance of renally cleared compounds as well as influence clearance of metabolcally cleared drugs
Hepatic impairment (HEP)	CL/F	Hepatic impairment may influence clearance of metabolically cleared drugs

a. Capsule type was explored in the base model

The effect of covariates on CL/F from the full PK model is shown in the table below. Capsule type, sex, and weight were significant covariates identified by the final model.

Table 16. Effects of covariates on total oral clearance of dabrafenib in the full model (Model 680)



Points represent relative value of PK parameter for the different covariates: bar represents 95% CI; shaded area represents a clinical difference of 20%; WT – body weight for range in the data set of 36.2 or 149.5 kg.

Capsule shell type was found to affect the bioavailability of dabrafenib. Dabrafenib CL/F was lower in female subjects compared to male subjects, and body weight influenced CL/F, Vc/F, and Q/F.

All non-significant covariates with 95% CI that included null values were then excluded from the model. The excluded effects were: age of 65-75 years, age > 75 years, mild renal impairment, moderate renal impairment, hepatic impairment, and inducers and inhibitors of CYP3A4 on CL/F; gender on Vc/F, and weight on Vp/F. The remaining covariates (capsule type, gender on CL/F, and weight on CL/F, Vc/F, and Q/F) were kept in the model.

The population PK model was evaluated using graphical assessment, assessment of degree of regression to the mean, estimates of precision of model parameters, predictive check techniques, and standardised visual predictive check plots. These checks demonstrated that the model adequately described the data, and no deficiencies were identified.

Model based simulations: Simulations based on the final population PK model were performed to: i) illustrate the time course of dabrafenib concentrations following 150, 100, 75, and 50 mg BID regimens administered in HPMC capsules after single dose, approach to steady-state (trough values, Ctrough), and at steady state; ii) illustrate the relationship between single dose and steady state exposure (Cmax, Ctrough, AUC(0-τ)) at these dose regimens; and iii) evaluate influence of significant covariates on single dose and the steady-state exposure at these dosing regimens.

Population PK analysis results: The parameters of the final covariate model are presented in the table below. These indicated that absorption, delayed by a short lag time (0.48 h) was generally fast (Ka = 1.9 h-1) but highly variable between subjects (CV=160%). Total CL/F was estimated using a non-inducible CL_0/F of 17.0 L/hr, and an inducible CL_{ind}/F at steady state following administration of dabrafenib 150 mg BID (HPMC capsules) of 17.3 L/hr, representing about half of the total CL/F. Therefore, total CL/F doubles with repeat dosing at this dose. Half-life of induction (i.e. time for inducible part of clearance to reach half its steady-state value) was 67 hours; thus steady state (5 half-lives) was reached after 14 days of dosing. The inter-individual variability was high: with CV of 59%, 53%, 99%, and 160%, for CL_0/F, Vc/F, Q/F, and Ka respectively. Intra-subject or residual variability was 53% (CV of the proportional error).

Table 17. Population PK parameter estimates of final PK model (Model 690)

Parameter		Estimate	%RSE	95%CI	Variability	Shrinkage
CL_0/F (L/hr)	θ_1	17.0	6.00	15 - 19		
V_C/F (L)	θ_2	70.3	5.48	62.7 - 77.8		
V_P/F (L)	θ_3	154	9.55	125 - 183		
Q/F (L/hr)	θ_4	3.30	7.32	2.82 - 3.77		
K_a (1/hr)	θ_5	1.88	10.2	1.5 - 2.25		
Tlag (hr)	θ_6	0.482	0.451	0.478 - 0.486		
$CL_{IND,SS}/F$ (L/hr)	θ_7	17.3	3.05	16.2 - 18.3		
Alpha	θ_8	0.927	4.67	0.842 - 1.01		
T_{50} (hr)	θ_9	67.3	15.2	47.2 - 87.3		
F_{GEL}	θ_{10}	0.555	6.14	0.488 - 0.622		
CLWT	θ_{11}	0.331	22.1	0.188 - 0.474		
CLSEX	θ_{12}	0.914	2.24	0.874 - 0.954		
VcWT	θ_{13}	0.384	31.1	0.15 - 0.617		
QWT	θ_{14}	1.22	24.4	0.637 - 1.8		
ω^2_{CL0}	$\Omega(1,1)$	0.343	11.1	0.268 - 0.418	CV=58.6%	24.5%
Covar ω_{CL}, ω_{Vc}	$\Omega(1,2)$	0.292	11.5	0.226 - 0.358	R =0.941	
ω^2_{Vc}	$\Omega(2,2)$	0.281	13.0	0.209 - 0.352	CV=53.0%	28.7%
ω^2_{Q}	$\Omega(3,3)$	0.980	13.0	0.729 - 1.23	CV=99.0%	32.6%
ω^2_{Ka}	$\Omega(4,4)$	2.57	9.74	2.08 - 3.06	CV=160%	29.4%
σ^2_{prop}	$\Sigma(1,1)$	0.28	3.27	0.262 - 0.298	CV=53.0%	9.6%
σ^2_{add} (ng/mL)	$\Sigma(2,2)$	17.6	13.5	13 - 22.3	SD=4.2	9.3%

Abbreviations: PE=Parameter Estimate; SE=Standard Error; %RSE= Relative Standard Error, %RSE=100·SE/PE; 95% CI= 95% confidence interval; SD=Standard Deviation computed as square root of the variance (=ω or =σ); CV= coefficient of variation, CV = 100*SD%; R = correlation coefficient; CL_0/F = apparent initial clearance; Vc/F = apparent volume of central compartment; Vp/F = apparent volume of peripheral compartment; Q/F = apparent inter-compartmental clearance; Ka = absorption rate constant; Tlag = absorption lag-time; $CL_{IND,SS}/F$ = apparent inducible clearance at steady state; Alpha = power of dependence of $CL_{IND,SS}$ on absorbed dose (LDOS*F_{GEL}); LDOS = last administered dose; F_{GEL} = relative bioavailability of gelatin capsule to HPMC capsule; T_{50} = half-life of clearance induction; ω^2_{CL0}, ω^2_{Vc}, $\omega^2_{Vp\_Part1}$, ω^2_{Q}, ω^2_{Ka} = variances of the respective inter-individual random effects; Covar = covariance; σ^2_{prop} = variance of the proportional component of the residual error model; σ^2_{add} = variance of the additive component of the residual error model.

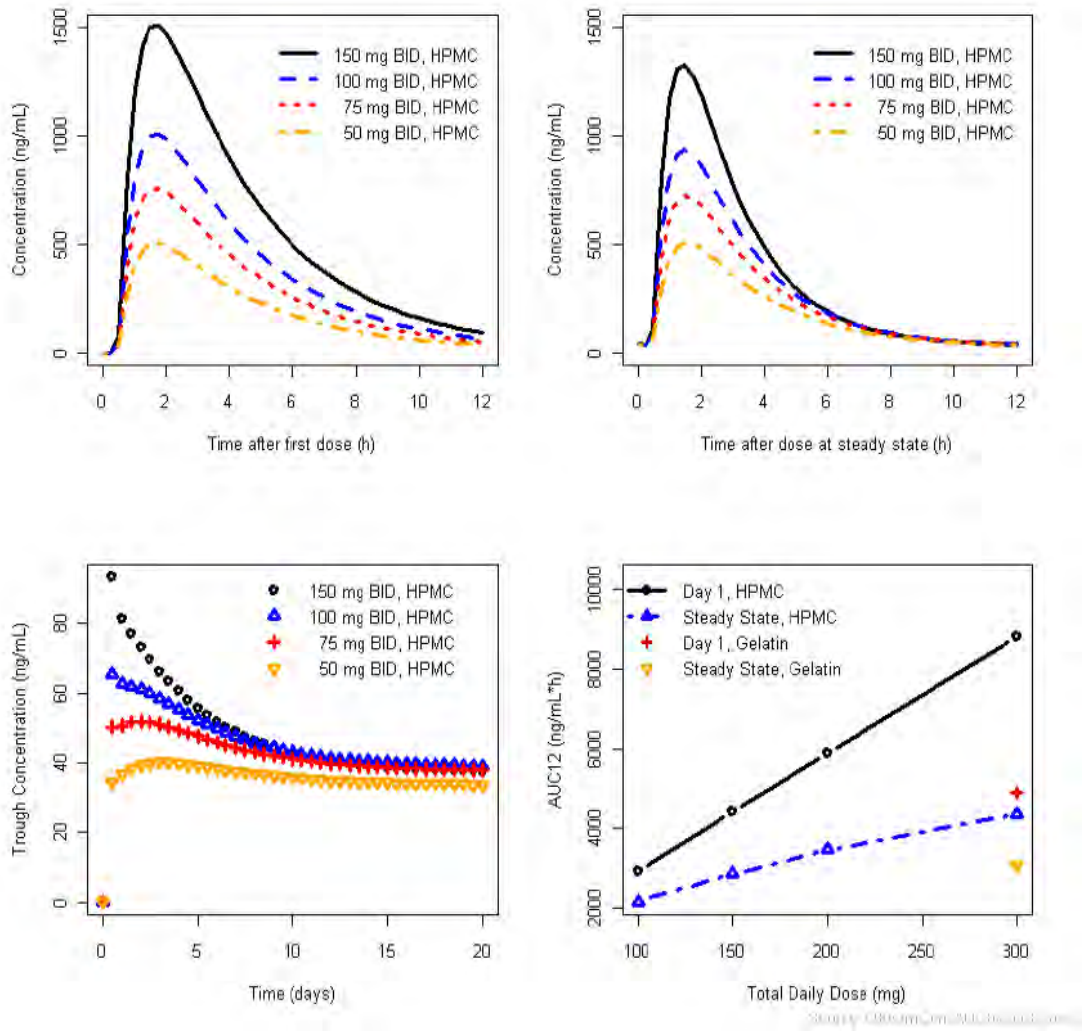
Using the final covariate PK model, the predicted PK profiles of dabrafenib following single and repeat dosing are summarised in the table below, and illustrated in the following figure.

Table 18. Typical dabrafenib exposure following single dose and at steady state with doses of 50, 75, 100 and 150mg BID

Total Daily Dose (mg)	Single Dose		Steady State			Steady State to Single Dose Ratio	
	Cmax (ng/mL)	AUC(0-τ) (ng/mL*h)	Cmax (ng/mL)	AUC(0-τ) (ng/mL*h)	Ctrough (ng/mL)	Cmax	AUC(0-τ)
300 (150 mg BID)	1512	8820	1324	4378	37.5	0.88	0.50
200 (100 mg BID)	1009	5880	936	3466	38.7	0.93	0.59
150 (75 mg BID)	757	4410	726	2876	37.6	0.96	0.65
100 (50 mg BID)	505	2940	503	2152	33.6	1.00	0.73

Typical exposure for 80 kg male subject who is administered 50, 75, 100 or 150 mg BID HPMC capsules

Figure 3. Predicted dabrafenib exposure (concentration profile, trough concentration or AUC (0-τ)) with doses of 50, 75, 100, and 150mg BID (HPMC capsules) for a typical 80kg male subject



Following administration of dabrafenib 150 mg BID (HPMC capsules), the ratios of steady-state AUC(0-τ) and Cmax to single dose values were 0.50 and 0.88, respectively. The extent of induction is lower at lower doses, evidenced by higher ratios at doses of 50mg BID. The bottom right plot of the figure shows that AUC(0-τ) was dose proportional on day one, but less than dose proportional on induction of clearance.

Comment: As this PK study did not include data from ongoing Study BRF113771, the dose proportionality findings do not include the most relevant and up-to-date data on the PK of dabrafenib using HPMC capsules following repeat dosing. The dose proportionality findings of Study BRF113771 (which found greater than dose proportionality with single dosing and dose proportionality with repeat dosing) are not consistent with the findings of this study, and therefore bring into question the accuracy of these results.

Through concentrations were initially proportional to dose, but decreased with time and were similar for all doses at steady state (approximately 40 ng/mL), appearing to plateau after 10 days of dosing, and reaching full steady state after 14 days.

Relative bioavailability of dabrafenib administered in gelatine capsules was 55.5% (48.8 - 62.2%) compared to HPMC capsules. The ratio of HPMC over gelatine capsules after single dose was predicted to be 1.80 for both Cmax and AUC(0-τ), as detailed in the table below. Following

induction with repeat dosing, the ratio of HPMC to gelatine decreased to 1.66 and 1.42 for Cmax and AUC(0-τ), respectively. There was no difference in Ctrough between HPMC and gelatine capsules.

Table 19. Typical dabrafenib exposure for HPMC and gelatine capsules

Capsule type	Single Dose		Steady State			Steady State to Single Dose Ratio	
	Cmax (ng/mL)	AUC(0-τ) (ng/mL*h)	Cmax (ng/mL)	AUC(0-τ) (ng/mL*h)	Ctrough (ng/mL)	Cmax	AUC(0-τ)
HPMC	1512	8820	1324	4378	37.5	0.88	0.50
Gelatin	840	4898	797	3084	38.2	0.94	0.63
Ratio HPMC/Gelatin	1.80	1.80	1.66	1.42	0.98	-	-

Typical exposure for 80 kg male who is administered 150 mg BID regimen as HPMC or gelatin capsule

Dabrafenib CL/F was 8.6% lower (95%CI: 4.6% - 12.6%) in female subjects relative to male subjects as shown in the table below. Although statistically significant, this difference was considered to be small and not clinically meaningful.

Table 20. Typical dabrafenib exposure for male and female subjects

	Day 1		Steady State		
	Cmax (ng/mL)	AUC(0-τ) (ng/mL*h)	Cmax (ng/mL)	AUC(0-τ) (ng/mL*h)	Ctrough (ng/mL)
Male	1512	8820	1324	4380	37.5
Female	1539	9650	1366	4791	47.1

Typical exposure for 80 kg male or female subject who is administered 150 mg BID HPMC capsules

Comment: It is agreed that this study shows that the difference in exposure to dabrafenib by gender does not appear to be clinically significant, and therefore differential dosing of dabrafenib by gender is not required.

Body weight influenced CL/F, Vc/F, and Q/F. PK parameters (shown in the table below) were predicted in a typical subject with low (50 kg) or high (140 kg) body weight and were shown to be within 20% of the value of a typical 80 kg subject. This difference was not considered by the sponsor to be clinically relevant.

Table 21. Typical dabrafenib exposure for subjects with different weight

Weight (kg)	Day 1		Steady State		
	Cmax (ng/mL)	AUC(0- τ) (ng/mL*h)	Cmax (ng/mL)	AUC(0- τ) (ng/mL*h)	Ctrough (ng/mL)
50	1824	10303	1576	5115	32.9
80	1512	8820	1324	4378	37.5
110	1327	7938	1175	3940	40.8
140	1200	7329	1072	3638	43.4

Typical exposure for a male subject with different body weight who is administered 150 mg BID HPMC capsules

Comment: It is noted that Cmax is 52% higher and AUC(0-τ) 41% higher after single dosing of dabrafenib for those with low body weight (50kg) compared to high body weight (140kg), and Cmax 32% higher and AUC(0-τ) 41% higher after repeat dosing at steady state. Therefore, the opinion of this evaluator is that PK difference with weight may potentially be clinically relevant, and warrants mention.

14.1.5. Evaluator's comments

There were some deficiencies in the design and conduct of this population PK analysis. The main limitation of this study was the analysis did not include the most recent data from ongoing

Study BRF113771, which has more rich-sampling data from repat doses of dabrafenib 150mg BID with HPMC capsules. It was found in Study BRF113468 that there was greater exposure to dabrafenib using HPMC vs. gelatine capsules. Since only Study BRF112680, which used gelatine capsules, had rich sampling data used in this analysis, this impacts on the accuracy and relevance of the results with respect to the proposed market formulation of dabrafenib using HPMC capsules. One main discrepancy in results between use of HPMC capsules (Study BRF113771) and gelatine capsules (Study BRF112680) was in dose proportionality. Therefore, the dose proportionality results of this analysis have been excluded from consideration. It is considered that differences in formulation are likely to have less impact on the differences observed in gender and weight as population PK model covariates, and thus these results have been included in the evaluation, although keeping in mind that the data is not fully up-to-date, and there may be inaccuracies.

Imprecision in the model estimates is likely to be exacerbated by the fact that three of the four studies included in the analysis only employed sparse sampling methods. In addition, 3% of samples were excluded from the analysis due to being 'outliers', without evaluation of the effect of their exclusion on the results.

The impact of these limitations is that the results of this population PK study could be considered imprecise and not including the most up-to-date results which are relevant to the proposed formulation. This needs to be taken into account in the interpretation of findings, and a repeat population PK study taking into account more recent study findings may be warranted.

Keeping these limitations in mind, reasonable conclusions drawn from this study (excluding that related to dose-dependency) are that:

- The PK of dabrafenib following oral administration to subjects with solid tumours is adequately described by a two-compartment model with first order absorption, absorption delay, and combined non-inducible and inducible oral clearance.
- CL/F consists of initial CL0/F and inducible component which is almost linearly related to dose. Total CL/F doubles with repeat dosing of dabrafenib at 150mg BID HPMC capsules.
- A prolonged terminal half-life of about 39 hours was calculated due to slow distribution. This may be overestimated by the model compared to half-life measured in other studies.
- Steady state is reached within 14 days. With a half-time of induction of 67 hours.
- The PK of dabrafenib is characterised by high inter-individual variability (53-160%)
- Bioavailability of dabrafenib administered as gelatine capsules was 45% lower compared to HPMC capsules.
- Of the explored covariates, gender and body weight were statistically significant. The effect of gender is not likely to be clinically relevant, however, the opinion of this evaluator is that the effect of body weight may potentially be relevant.
- Age, mild and moderate renal impairment, mild hepatic impairment, and concomitant use of mild CYP3A4 inducers and inhibitors did not influence the PK of dabrafenib.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au