27 June 2013
EMA/CHMP/242419/2013/corr 1
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Tafinlar

International non-proprietary name: DABRAFENIB

Procedure No EMEA/H/C/002604/0000

Note

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

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Product information

Name of the medicinal product:	Tafinlar
Applicant:	GlaxoSmithKline Trading Services Limited 6900 Cork Airport Business Park Kinsale Road Cork Republic of Ireland
Active substance:	DABRAFENIB MESILATE
International Nonproprietary Name/Common Name:	DABRAFENIB
Pharmaco-therapeutic group (ATC Code):	Antineoplastic agents, protein kinase inhibitor L01XE23
Therapeutic indication:	Dabrafenib is indicated in monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation
Pharmaceutical form:	Capsule, hard
Strengths:	50 mg and 75 mg
Route of administration:	Oral use
Packaging:	bottle
Package sizes:	28 capsules and 120 capsules

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ASMF	Active Substance Master File
ATP	Adenosine triphosphate
ATS	All Treated Subjects
BCS	Biopharmaceutics Classification System
BID	Twice daily
BREAK-2	Study BRF113710
BREAK-3	Study BRF113683
BREAK-MB	Study BRF113929
BSE	Bovine spongiform encephalopathy
CHMP	Committee for Human Medicinal Products
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CQA	Critical Quality Attribute
CR	Complete response
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
CSR	Clinical study report
DTIC	Dacarbazine
ECOG PS	Eastern Cooperative Oncology Group performance status
EORTC	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
eCRF	Electronic case report form
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FFPE	Formalin-fixed paraffin-embedded
FITH	First time in human
FMEA	Failure Mode and Effects Analysis
GC	Gas Chromatography
HDPE	High Density Polyethylene
HPLC	High pressure liquid chromatography
HPMC	Hydroxypropyl methylcellulose
HR	Hazard ratio
HRQOL	Health-related quality of life
IC_{50}	Concentration causing 50% inhibition
ICH	International Conference on Harmonisation
IFN-a	Interferon-alpha
IL-2	Interleukin 2
IR	Infrared
IRC	Independent Review Committee
ITT	Intent-to-treat
IUO	Investigational use only
KF	Karl Fisher
LDH	Lactate dehydrogenase
LDPE	Low Density Polyethylene
MOA	Mode of action
MRI	Magnetic resonance imaging
NE	Not evaluated
NR	Not reached
OIRR	Overall intracranial response rate
ORR	Overall response rate
OS	Overall survival
PAR	Proven Acceptable Ranges
PCR	Polymerase chain reaction
PD	Progressive disease

pERK	Phosphorylated extracellular signal-related kinase
PFS	Progression-free survival
Ph.Eur	European Pharmacopoeia
PP	polypropylene
PPE	Palmar-Plantar Erythrodysesthesia
PR	Partial response
PS	Performance status
PVC	Polyvinyl Chloride
QbD	Quality by design
QTTP	Quality target product profile
RAP	Reporting analysis plan
RECIST	Response Evaluation Criteria In Solid Tumors
RH	Relative humidity
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SD	Stable disease
SRS	Stereotactic radiosurgery
TSE	Transmissible Spongiform Encephalopathy
Vs	Versus
WBRT	Whole body radiotherapy

1. Background information on the procedure

1.1. Submission of the dossier

The applicant GlaxoSmithKline Trading Services submitted on 24 July 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Tafinlar, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 June 2011.

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

The legal basis for this application refers to:

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

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0024/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (European Medicines Agency decision

P/0024/2012) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

The application did not contain a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products.

New active Substance status

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

Scientific Advice

The applicant received Scientific Advice from the CHMP in November 2011. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

Tafinlar has given a Marketing Authorisation in the USA on 29 May 2013.

Manufacturer responsible for batch release

GLAXO WELLCOME, S.A.
Avda. Extremadura, 3, Pol. Ind. Allendeduero
Aranda de Duero, Burgos, 09400
Spain

1.2. Steps taken for the assessment of the product

- The application was received by the EMA on 24 July 2012.
- The procedure started on 15 August 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 5 November 2012 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 2 November 2012 (Annex 2).
- During the meeting on 13 December 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 14 December 2012 (Annex 4).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 February 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 March 2013 (Annex 5).
- During the CHMP meeting on 25 April 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 6).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 May 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 10 June 2013 (Annex 8).
- The Rapporteurs circulated the Updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 19 June 2013 (Annex 9).
- During the meeting on 27 June 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Tafinlar.

2. Scientific discussion

2.1. Introduction

Problem statement

Cutaneous melanoma is the most aggressive form of all skin cancers, with approximately 132,000 new cases and approximately 37,000 disease-related deaths worldwide each year. Historically, the median survival time for subjects with stage IV melanoma was approximately 6 months with 26% of subjects alive at 1-year (1). The estimated 5-year survival rate was <10%, with median Progression Free Survival (PFS) of 1.7 months (2).

For decades, cytotoxic chemo- and immunotherapy have been the mainstays of systemic therapy for unresectable melanoma. However, the response rate of chemotherapy is low (approximately 10%), and only few melanoma patients achieve a more durable tumour control (3). For metastatic disease, dacarbazine (dimethyl triazene imidazole carboxamide or DTIC) was the first approved treatment for metastatic melanoma with observed responses ranging from 10 to 12%, median PFS of approximately 1.5 months, and median Overall Survival (OS) of 6.4 months (4).

The therapeutic landscape for the treatment of metastatic melanoma has recently changed significantly with the regulatory approval of two new active agents, ipilimumab and vemurafenib.

Ipilimumab was granted a marketing authorisation for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy as it improved median OS compared to gp10. Vemurafenib was granted a marketing authorisation for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma based on the improved median OS and PFS compared to dacarbazine.

About the product

The RAS/RAF/MEK/ERK pathway is a critical proliferation pathway in many human cancers. This pathway can be constitutively activated by alterations in specific proteins, including BRAF, which phosphorylates MEK1 and MEK2 on two regulatory serine residues. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 30 to 60% of melanoma (5,6). BRAF V600E mutation is the most common (~80 to 90%) (7) followed by V600K (~10 to 20%). A number of rare substitutions also occur including V600D, V600G, V600M and V600R.

Dabrafenib is an inhibitor of RAF kinases. Oncogenic mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway. Dabrafenib inhibits BRAF kinases with activating codon 600 mutations.

Dabrafenib showed suppression of a downstream pharmacodynamic biomarker (phosphorylated ERK) and inhibited cell growth of BRAF V600 mutant melanoma cell lines, *in vitro* and in animal models. In subjects with BRAF V600 mutation positive melanoma, administration of dabrafenib resulted in inhibition of tumour phosphorylated ERK relative to baseline.

The Applicant applied for the indication: ‘‘Dabrafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation’’.

The CHMP adopted a positive opinion for the following indication:

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

Dabrafenib is administered orally and it is available as 50 mg and 75 mg capsules. The recommended dose of dabrafenib is 150 mg (two capsules of 75 mg) twice daily (corresponding to a total daily dose of 300 mg). Dabrafenib should be taken at least one hour before, or at least 2 hours after a meal, and leaving an interval of approximately 12 hours between doses. Dabrafenib should be taken at similar times every day to increase patient compliance.

2.2. Quality aspects

2.2.1. Introduction

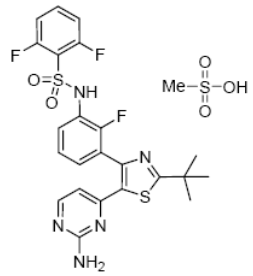
Tafinlar is presented as hypromellose capsules containing either 50 mg or 75 mg dabrafenib as active substance, which corresponds to 59.25 mg and 88.88 mg dabrafenib mesylate, respectively per capsule.

Other ingredients are: microcrystalline cellulose, magnesium stearate and colloidal silicon dioxide. The capsule shell consists of hypromellose, red iron oxide, titanium dioxide. The printing ink contains shellac, black iron oxide, n-butyl alcohol, isopropyl alcohol, propylene glycol and ammonium hydroxide. The list of excipients can be found in section 6.1. of the SmPC.

The capsules of the two strengths can be distinguished by size, color and identifying codes. The product is packaged in HDPE bottles with PP closures and contains a silica desiccant.

2.2.2. Active substance

Dabrafenib mesylate is a white to slightly coloured powder, it is not hygroscopic and is practically insoluble in aqueous media at pH 4-8 and only very slightly soluble at pH 1. The active substance meets the criteria for Biopharmaceutics Classification System (BCS) Class II (low solubility and high permeability). Dabrafenib mesylate converts to its free base in aqueous media. The chemical name of dabrafenib mesylate is:
N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzene sulfonamide, methanesulfonate salt. It has the following structural formula:



Dabrafenib mesylate has no chiral centers and hence exhibits no stereoisomerism. Polymorphism has been observed for dabrafenib mesylate and the crystalline form (Form 1) is used to manufacture the medicinal product in view of its solubility and stability. The ASMF procedure has not been used for this marketing authorisation application and there is no monograph for dabrafenib in the European Pharmacopoeia.

Manufacture

Dabrafenib mesylate is supplied by one manufacturer. The synthesis consists of four stages, three of which involve the breaking and/or formation of covalent bonds. The fourth stage is the salt formation, followed by a micronization step. Dabrafenib mesylate is micronized to achieve the desired particle size distribution. This is important for the bioavailability of the medicinal product.

Sufficient information has been provided on the manufacturing process development. The critical steps have been identified and proven acceptable ranges have been established for the critical and non-critical process parameters in all four stages of the manufacturing process. A risk assessment (FMEA) has been performed to identify the critical process parameters and proven acceptable ranges (PARs) have been set The PARs were established at laboratory and pilot scale but this was considered acceptable for operation at commercial scale because the processes are scale independent.

Adequate specifications and control methods for intermediates, starting materials and reagents have been presented and adequate in-process controls are in place. The proposed starting materials are well defined and have acceptable specifications. Batch analysis data have been provided for six production scale batches and demonstrate that the active ingredient can be manufactured reproducibly.

Elucidation of the chemical structure of dabrafenib mesylate is supported by the synthetic route and has been verified through spectroscopic measurements and elemental analysis. The crystal and molecular structure of dabrafenib mesylate Form 1 has been determined by three-dimensional single crystal X-ray diffraction measurements. The formation of and potential carry-over of genotoxic compounds to the final drug substance have been adequately addressed. None of the genotoxic impurities will be carried over to the drug substance at levels exceeding the threshold of toxicological concern.

Dabrafenib mesylate is packaged in LDPE bags. The specifications for the LDPE bags are appropriate for this active substance.

Specification

The active substance specification includes tests for: appearance, identity (IR), assay (HPLC, 98.0 – 102.0%), impurities (HPLC), residual solvents (GC), water content (KF), residue on ignition, sulphated ash and particle size (laser diffraction). The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines.

Some of the tests are performed on the non-micronized substance, others on the micronized substance. It has been shown that micronization of the dabrafenib mesylate has no effect on the drug related impurities, so it is acceptable to perform the analysis on either non-micronized or micronized drug substance.

The identity is determined by IR spectroscopy which has been shown specific and can discriminate between the dabrafenib free base, dabrafenib mesylate, dabrafenib mesylate hydrate, and other polymorphs of dabrafenib, at least for the pure substances. A justification has been provided for not including a test for heavy metals and for microbiological quality in the drug substance specification.

Batch analysis data have been provided for six production-scale batches of dabrafenib mesylate, which were manufactured according to the proposed commercial route at the commercial site and tested by the proposed commercial methods. Three of the batches were micronized. The results are within the specifications and consistent from batch to batch. The proposed specifications for the drug substance are adequately justified and supported by batch analysis data and stability data.

Stability

Stability studies have been initiated according to the ICH guidelines on three production scale batches of micronized dabrafenib mesylate manufactured according to the proposed commercial process and stored in a package representative of the commercial package. Six months of accelerated (40ºC/75%RH) and twelve months of long term (25ºC/60%RH) stability data have been provided. No significant change has been observed in any of the parameters studied, all results were within the proposed specifications. One of the primary batches has also been included in a photo-stability study according to ICH Q1B. Forced degradation studies have also been performed on dabrafenib mesylate in the solid state and in solution.

The following parameters were tested: appearance, drug content, drug related impurities, water content and particle size. The analytical methods used were the same as for release or equivalent, and are stability indicating.

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

2.2.3. Finished Medicinal Product

Pharmaceutical development

The aim of the development was to achieve an immediate release dosage form of dabrafenib for oral administration. Two strengths have been developed, containing 50 mg and 75 mg dabrafenib (as free base), respectively. The pharmaceutical development contains some QbD elements. The quality target product profile (QTPP) was defined as an immediate release dosage form, which can be swallowed easily, allows flexible dose adjustments for patients, that meets compendial and other relevant quality standards, and is packaged protected from moisture.

The critical quality attributes (CQA) of the product which may have impact on the efficacy and safety of the drug product have been defined as description, identification and content of active substance, drug related impurities, uniformity of dosage units, dissolution, particle size, capsule description and capsule moisture. The particle size of the drug substance is a CQA because of its potential impact on bioavailability. A test for the particle size is included in the drug substance specifications.

In early clinical development, low doses (1 mg, 5 mg) of dabrafenib capsules were used and hence the particle size of the drug substance was considered to be critical with regard to content uniformity, and therefore the dabrafenib mesylate was micronized. Later, when higher doses (50 mg and 75 mg) were developed, micronization was maintained because there were then no pharmacokinetic data which supported the use of non-micronized substance. Initially, hard gelatine capsules were used for the formulation but due to a decreasing dissolution rate during stability, it was decided to develop Tafinlar in hypromellose capsules with lower moisture content. Hypromellose capsules with a composition identical to the one proposed for marketing have been used for the Phase 3 clinical studies.

The manufacturing process development has been described in sufficient detail. The objective was to formulate a simple blend that would be suitable for capsule filling using either gravity fed manual filling or a dosator type encapsulation machine. The applicant has applied relationship matrices, Input Process Output (IPO) diagrams and Failure Mode and Effects Analysis (FMEA) to establish the process parameters and attributes that have the greatest impact on drug product quality and to develop an adequate control strategy. Critical process parameters and CQAs have been adequately identified.

Standard excipients have been selected for the capsule formulation: microcrystalline cellulose (diluent), magnesium stearate (lubricant) and colloidal silicon dioxide (glidant). The capsule shell consists of hypromellose (capsule matrix), red iron oxide (colourant), titanium dioxide (opacifier) and printing ink. The printing ink contains shellac, black iron oxide, n-butyl alcohol, isopropyl alcohol, propylene glycol and ammonium hydroxide. Tafinlar does not contain excipients which require a special warning in section 2 of the SmPC.

The capsules are packaged in white HDPE bottles with plastic closures. A desiccant canister is included in the bottles. The HDPE bottle complies with the Ph.Eur. (for polyolefins) and the plastic packaging material complies with the Commission Regulation (EU) No. 10/2011 for plastic materials intended to come into contact with food. The container closure system is adequate to support the stability and use of the product.

Adventitious agents

No excipients derived from animal or human origin have been used. Shellac, used in the printing ink on the capsules, is derived from insects which are not covered by BSE/TSE regulations. Magnesium stearate is of vegetable origin.

Manufacture of the product

The manufacturing process of Tafinlar is considered to be a standard process. The main steps include: i) powder blending, ii) low shear lubrication and iii) capsule filling. The encapsulation has been identified as a critical step. A detailed description of the manufacturing process has been provided and adequate in-process controls are in place. The in-process controls include a test for the mean capsule fill weight, individual capsule fill weight, length of closed capsule, and capsule appearance. No intermediates are involved in the manufacturing process. The manufacturing process has been validated on 10 and 19 commercial scale batches of 50 mg and 75 mg capsules, respectively, according to the proposed commercial manufacturing process. The results demonstrate that the process is capable to reproducibly produce the finished product of the intended quality.

Product specification

The finished product release and shelf-life specifications include appropriate tests for appearance, identity (HPLC, UV), assay (95.0% - 105.0% of label claim by HPLC), uniformity of dosage units (by weight variation, Ph.Eur.), impurities (HPLC), dissolution (UV) and microbial limits. The tests for impurities and microbial limits are performed at shelf-life only.

No test for water content is proposed and this is considered acceptable since moisture is controlled by the capsule shells and the product is packaged with a desiccant canister.

Stability of the product

Stability data of 3 production scale batches have been presented for each strength. Up to 12 months stability data produced under long term conditions (25ºC/60%RH) and up to 6 months data under accelerated conditions (40ºC/75%RH) have been provided, according to the ICH guideline. The batches were packaged in the commercial package with desiccant and were manufactured by the commercial process.

The following parameters were tested in the stability studies: appearance, dabrafenib content, drug related impurities, dissolution, water content and microbiological quality. The same methods as used for release testing are used for stability testing.

Photo-stability stress testing was performed for one batch of each strength, in line with the ICH Q1B guideline. No significant change in the parameters studied was observed after light exposure of the dabrafenib capsules.

Furthermore, the 50 mg and 75 mg capsules have also been subjected to some forced degradation in order to identify potential degradation products. The stressed conditions are: heat, heat and humidity, UV exposure and fluorescent light exposure. The capsules were analysed for related substances by HPLC after the forced degradation treatment and the analytical method demonstrated to be stability indicating.

Based on available stability data, the proposed shelf-life and as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

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

At the time of the CHMP opinion, there were no unresolved quality issues having an impact on the Benefit/Risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Non-clinical studies were conducted in mice, rats, monkeys, rabbits and dogs.

All pivotal safety studies were carried out in compliance with GLP regulations.

The toxicological evaluation of dabrafenib has been conducted in accordance with the guidance in ICH S9.

The Applicant received Scientific Advice from the CHMP pertaining to non-clinical aspects of the dossier and more specifically on the adequacy of the non-clinical data package to support the Marketing Authorisation Application.

2.3.2. Pharmacology

Primary pharmacodynamic studies

***In vitro* studies – potency, mechanism of action and selectivity**

The *in vitro* activity of dabrafenib was evaluated utilizing a baculovirus or transient mammalian expression system to produce wildtype (WT) human BRAF and CRAF, as well as $BRAF^{V600E}$, $BRAF^{V600K}$ and $BRAF^{V600D}$ mutant full length active enzymes or truncated constitutively active human CRAF. Dabrafenib inhibited human wildtype BRAF and CRAF enzymes with IC_{50} values of 3.2 and 5.0 nM, respectively, as well as the mutant forms $BRAF^{V600E}$, $BRAF^{V600K}$ and $BRAF^{V600D}$, having IC_{50} values of 0.65, 0.5 and 1.84 nM, respectively.

The IC_{50} values for dabrafenib for WT BRAF orthologues from human, monkey, dog and rat were 4.8, 4.1, 4.3 and 4.0 nM, respectively, demonstrating similar activity against nonclinical species and supported the use of rats and dogs as the species for toxicology studies. Other analyses showed that dabrafenib is a time-dependent, reversible inhibitor of WT BRAF and $BRAF^{V600E}$ enzymes, and is an ATP competitive inhibitor of WT BRAF and CRAF and $BRAF^{V600E}$. Three active dabrafenib metabolites have been identified, with two metabolites (desmethyl-dabrafenib and hydroxy-dabrafenib) demonstrating potent inhibition of WT BRAF and CRAF and mutant BRAF kinases, and one metabolite (carboxy-dabrafenib) showing reduced activity against these enzymes (13- to 47-fold). The dabrafenib metabolites also showed similar activities against rat, dog and monkey WT BRAF compared to their respective values on the human orthologue (Table 1).

Table 01 Relative inhibitory activity of dabrafenib and metabolites

Target/Species	Dabrafenib (Parent)	Hydroxy-Dabrafenib	Carboxy-Dabrafenib	Desmethyl-Dabrafenib
Relative Inhibitory Activity Against Human BRAF and CRAF Kinases				
WT BRAF Truncated CRAF	1.0 1.0	5.6 5.6	46.5 20.5	1.5 1.2
Relative Inhibitory Activity Against WT BRAF Orthologues				
Human Rat Dog Monkey	1.0 1.0 1.0 1.0	6 7 6 6	47 55 55 50	1 2 2 2
IC_{50} Values (nM) for Inhibition of V600 BRAF Mutants				
$BRAF^{V600E}$ $BRAF^{V600K}$ $BRAF^{V600D}$	0.65 0.50 1.84	1.9 1.3 6.3	16.6 6.3 50.1	1.12 0.56 2.75

MEK and ERK are downstream substrates of RAF kinases, and inhibition of BRAF activity in cells containing mutant $BRAF^{V600E}$ is expected to result in decreased phosphorylation of MEK and ERK (Figure 1).

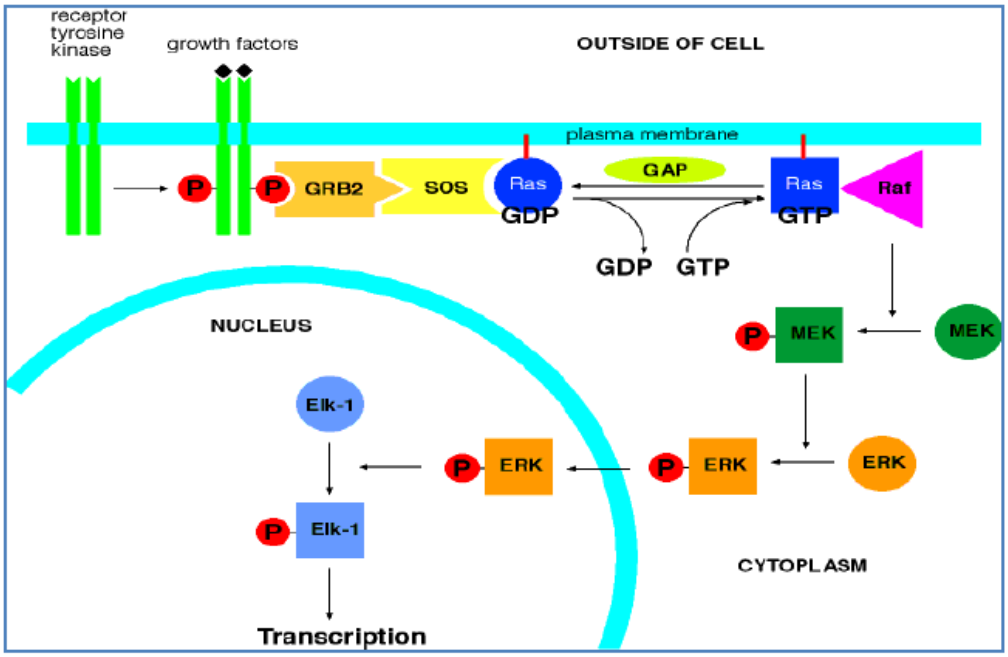


Figure 01 The RAS/RAF/MAP Kinase (ERK) Signal Transduction Pathway

Treatment of ES-2 ovarian carcinoma cells, containing $BRAF^{V600E}$ mutant, with dabrafenib for 1 hour resulted in a concentration-dependent decrease in pERK and pMEK, with no change in total ERK and MEK protein levels (data not shown). Treatment of various $BRAF^{V600E}$ cell lines with dabrafenib resulted in potent inhibition of pERK, including the melanoma cell lines A375PF11s and SK-MEL-28, but not in cell lines containing WT BRAF or mutated RAS proteins, using in-cell Western, Western blot assays or ELISA assays (data not shown).

The IC_{50} values for inhibition of ERK phosphorylation and inhibition of cell proliferation in SK-MEL-28 melanoma cells by dabrafenib were comparable (Tables 2 and 3). The 3 metabolites (hydroxy-dabrafenib (M7), desmethyl-dabrafenib (M8), and carboxy-dabrafenib (M4) were also examined. Whereas hydroxy-dabrafenib and desmethyl-dabrafenib had similar potency as dabrafenib, carboxy-dabrafenib was 17-fold less potent in inhibition of ERK phosphorylation, and 37-fold less potent in inhibition of cell proliferation (Table 2).

Table 02 Cellular pERK Inhibition by Dabrafenib and Metabolites

Assays	parent GSK2118436	M7 GSK2285403	M4 GSK2298683	M8 GSK2167542
pERK (SK-MEL-28) 10% FBS (IC_{50}, nM)	9	7	156	8

Table 03 Antiproliferative Activity of Dabrafenib and Metabolites is Specific to Activated BRAF Mutant Cell Lines

Assays proliferation gIC50, nM	parent GSK2118436	M7 GSK2285403	M4 GSK2298683	M8 GSK2167542
SK-MEL-28	6	17.7	223	9
Colo205	6	23	320	23
HN5	>20000	>20000	>20000	>20000

In HCT116, a human colon carcinoma cell line containing mutated RAS, dabrafenib and hydroxy-dabrafenib did not show anti-proliferative activity, and dabrafenib and its 3 metabolites were also unable to inhibit HN5 tumour cells (head and neck squamous carcinoma) with WT BRAF and RAS.

The duration and reversibility of pERK inhibition in SK-MEL-28 cells were investigated after compound removal following treatment with dabrafenib (300 nM, 33-fold the pERK IC_{50}) for 2 hours. The inhibition of pERK formation persisted for 4 hours with complete recovery by 6 hours post-compound removal.

The ability of dabrafenib to inhibit proliferation of >110 human tumour cell lines, each with confirmed BRAF mutational status, was evaluated in a 3 day growth assay. Sensitivity to dabrafenib significantly correlated with the presence of $BRAF^{V600E}$ with 16 out of 18 cell lines with IC_{50}s <100 nM containing $BRAF^{V600E}$. Furthermore, dabrafenib inhibited proliferation of 73% of the $BRAF^{V600E}$ containing cell lines, but generally showed little to no activity against all other cancer cell lines tested. Thirteen out of 15 $BRAF^{V600E}$, 4 out of 5 $BRAF^{V600K}$ and 1 out of 1 $BRAF^{V600D}$ melanoma cell lines were sensitive to cell growth inhibition by dabrafenib (IC_{50} <1 μM) (data not shown).

Yancovitz et al. reported that in any given tumour, the relative frequency of the BRAF V600E mutation ranged from 0% (indicating wildtype) to 48.3% for one patient tumour, whereas in another case the range was 4.9%-81.2%.

The reversibility of cell growth arrest was shown in SK-MEL-28 melanoma cells following treatment with dabrafenib and removal of the compound allowing regrowth after re-plating. The cells showed noticeable regrowth after 3 and 4 days, indicating that sustained compound presence might be required for prolonged tumour growth inhibition.

In SK-MEL-28 and A375PF11s human melanoma cell lines containing the $BRAF^{V600E}$ mutation, dabrafenib treatment was able to induce a concentration-dependent G_0/G_1 cell cycle arrest and some apoptosis. In contrast, HN5, a head and neck squamous carcinoma cell line containing wildtype BRAF and RAS, as well as normal human fibroblast cells, were not susceptible to either significant G_0/G_1 arrest or the induction of apoptosis, reflecting the previously observed lack of sensitivity of these cells to dabrafenib in the cell growth assays. In conclusion, dabrafenib potently decreased pERK through inhibition of BRAF mutant kinases and was a selective inhibitor of BRAF mutant cancer cell proliferation.

In additional studies mechanisms involved in development of resistance and combinations to treat and delay the emergence of resistance were investigated. The $BRAF^{V600E}$ melanoma cell line A375PF11s or the $BRAF^{V600K}$ melanoma cell line YUSIT-1 were exposed to increasing concentrations of dabrafenib and a drug-resistant population was selected. Clones were isolated that were 35-fold less sensitive or insensitive to cell growth inhibition by dabrafenib. Genetic characterization of the resistant clones identified an in-frame deletion in MEK1 ($MEK1^{K59del}$) or NRAS mutation ($NRAS^{Q61K}$ and/or $NRAS^{A146T}$) with and without $MEK1^{P387S}$ in the $BRAF^{V600E}$ background and $NRAS^{Q61K}$ in the $BRAF^{V600K}$ background. In the resistant clones dabrafenib reduced phosphorylation of MEK; however, it did not decrease phosphorylation of either ERK or S6P, or the levels of cyclin D1 protein. Combined inhibition of both BRAF and MEK kinases with dabrafenib and trametinib (a MEK inhibitor) effectively suppressed signalling and gene expression related to an activated RAF-MEK-ERK pathway, thereby reducing cell proliferation in a similar manner as observed in dabrafenib-treated parental cells. Further studies showed that cell lines containing mutant BRAF and that were PTEN null were less efficiently growth inhibited by dabrafenib than cell lines that were PTEN WT. PTEN null cell lines had higher basal phosphorylation of Akt than cells that were PTEN WT, and treatment with dabrafenib increased Akt phosphorylation in PTEN null cell lines. In PTEN null cell lines, the combination of dabrafenib and a PI3K/mTor inhibitor was more effective than the combination of dabrafenib and the MEK inhibitor.

Secondary pharmacodynamic studies

A study was conducted to investigate potential off-target activity of dabrafenib against a broad panel of proteins. In this study, dabrafenib (concentrations up to 5 μM) was tested *in vitro* against a variety of proteins which include fourteen 7-transmembrane receptors, two enzymes, seven ion channels, four kinases and three transporter molecules. Dabrafenib had no inhibiting or activating effect on the majority of proteins tested in these assays (XC_{50} >5 μM). Dabrafenib showed moderate potency (0.3-3.2 μM) against the α_{2C}-adrenergic receptor (EC_{50} >0.3 μM) and inhibition of LCK (IC_{50} >0.6 μM), GSK3β (IC_{50} >0.8 μM) and Aurora B kinases (IC_{50} >3.2 μM). All activities against these proteins were at least 100-fold less potent than against BRAF enzymes.

Safety pharmacology programme

Results of safety pharmacology studies are summarised in table 4.

Table 04 Safety Pharmacology Studies with Dabrafenib

Type of Study	Species (Strain) Method of Administration	Dose (mg/kg) Concentration	Findings
Neurobehavioral VD2008/00869/00 GLP	Rat (Sprague Dawley) Oral (gavage)	5, 20, 200	No adverse effects on neurobehavioral function or affect body temperature in the male rat following a single oral administration of dabrafenib.
Respiratory CD2008/01279/00 GLP	Rat (Sprague Dawley) Oral (gavage)	5, 20, 200	No adverse effect on respiratory function or body temperature in the male rat.
hERG Fluorescence Polarization assay UH2010/00045/01 Non-GLP	CHO-S1 hERG membranes *In vitro*	0.85 to 50 μM	Dabrafenib, hydroxy-dabrafenib and desmethyl-dabrafenib did not inhibit the capacity of labelled dofetilide (hERG inhibitor) to bind hERG (pIC_{50} <4.3)
Patch Xpress hERG assay UH2010/00045/01 Non-GLP	HEK293 cells *In vitro*	up to 150 μM	Dabrafenib and the hydroxy-, carboxyl- and desmethyl- metabolites when investigated up to their limits of solubility did not inhibit hERG (IC_{50} values of 48, >30, >150 and 56 μM, respectively).
hERG assay FD2008/00376/00 GLP	HEK293 cells *In vitro*	1.5, 5, 15, 30[a] μM	Concentration-dependent inhibition of hERG tail current recorded in these cells. The IC_{25} value was estimated to be 11.7 μM (6.1 μg/mL). Insufficient inhibition occurred to allow reliable estimation of IC_{50} or IC_{75} values.
Ventricular wedge assay UD2009/00043/00 Non-GLP	Rabbit *In vitro*	1, 3, 10, 30 μM	QT interval shortening (29.7% at 30 μM), a 47.1% reduction in transmural dispersion of repolarization (T_{p-e}) at 30 μM and no torsadogenic potential, as evidenced by a negative TdP score of -2 (scores >3 indicate torsadogenic potential). A concentration-dependent decrease in contractile force was observed (maximum 64% at 30 μM).

Cardiovascular CD2008/01717/00 Non-GLP	Rat (Sprague Dawley) Oral (gavage)	5, 20, 200	Dose-dependent, mild to moderate increase in heart rate (up to 48 beats/ minute or 18%). The increased heart rate was evident between 2 and 7 hours post dose at 5 mg/kg. A sustained increase in heart rate was noted between 2 and 24 hours post dose for doses ≥20 mg/kg. There was no effect on arterial blood pressures or body temperature.
Cardiovascular CD2008/01280/00 GLP	Dog (beagle) Oral(gavage)	1, 5, 50	At 50 mg/kg: a mild, reversible increase in heart rate (up to 18 beats/minute or 28%) and a mild, reversible decrease in PR interval duration (up to 7 msec or 7%). No electrocardiographic waveform abnormalities, arrhythmias or effects on body temperature at any dabrafenib dose.

Pharmacodynamic drug interactions

No relevant studies were submitted (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

The pharmacokinetic studies have been conducted with different forms of dabrafenib. Micronized dabrafenib mesylate is the form intended for human use. However, the majority of nonclinical studies were conducted with the micronized dabrafenib free base, as a stable suspension formulation of the mesylate salt was not available.

Absorption and systemic bioavailability was studied in male rats, mice, dogs, and monkeys. Dabrafenib had moderate blood clearance in the mouse (43.5 % of liver blood flow), rat (32 % of liver blood flow) and monkey (50 % of liver blood flow) and low blood clearance in the dog (12 % of liver blood flow). Steady state volume of distribution was low to moderate in all species (0.6-1.4 times total body water). Bioavailability ranged from 46 % in monkeys to 70% in mice, 77% in rats, and 82% in dogs following low oral doses. Terminal half-life was 0.3h in mouse and monkeys, 0.7h in rats and 2.8h in dogs.

In rats administered 5 or 10 mg/kg dabrafenib (micronized anhydrate/Form 2) as a single oral dose, showed that systemic exposure (plasma AUC and C_{max}) was unchanged following a 2-fold increase in dose. Following administration of micronized dabrafenib mesylate in 0.5% HPMC (stable suspension formulation) at 20 mg/kg, for a 2-fold increase in dose there was a >4-fold and >10-fold increase in AUC and C_{max}, respectively, as compared to the 10 mg/kg dose of dabrafenib administered as a suspension.

In bile duct cannulated (BDC) rats, oral absorption of 14C-dabrafenib was 35.7% based on the total radioactivity eliminated in urine and bile.

In an oral dose range toxicity study, male and female rats (3/sex/group) received oral doses of dabrafenib mesylate at 20, 200, 400 or 600 mg/kg. Plasma samples were collected for the first 24 hours after dosing, and showed less than proportional increase in mean dabrafenib exposure.

In dogs, micronized dabrafenib (Form 2) was administered in oral suspension at a dose level of 5 mg/kg or 10 mg/kg, 10 mg/kg in gelatine capsules, and dabrafenib mesylate was administered at a dose of 10 mg/kg in gelatine capsules or in suspension. Exposure levels were higher when the mesylate form was administered, and the suspension resulted in higher exposure than capsules.

In mice, the plasma toxicokinetics of dabrafenib, hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib were determined following oral repeat dosing of dabrafenib at 100, 300 and 1000 mg/kg/day for 14 days. Systemic exposure (AUC and Cmax) to dabrafenib was similar in males and females at each dose and increased less than dose-proportionally. Systemic exposure to hydroxy-dabrafenib was approximately equal to dabrafenib in the females and ~0.5X in males, while systemic exposure to carboxy-dabrafenib and desmethyl-dabrafenib was notably greater than dabrafenib at each dose.

For evaluation of potential penetration of circulating metabolites into select tissues (i.e., brain, liver, kidney and xenograft tumor), a pharmacokinetic/tissue distribution (PK/TD) study was conducted as part of a repeat dose pharmacodynamic (PD) study in the mouse. In mice bearing A375pF11s xenograft tumors, exposure (AUC_{0-t}) to hydroxy-dabrafenib was lower than dabrafenib in all tissue homogenates tested, except for liver in which hydroxy-dabrafenib exposure was approximately 2-fold higher than dabrafenib. Matrix –assisted laser desorption/ionization (MALDI) imaging mass spectrometry (IMS) of 2 hour mouse livers revealed that dabrafenib and hydroxy-dabrafenib were distributed throughout the liver, while carboxy-dabrafenib and desmethyl-dabrafenib were confined to the bile duct regions. MALDI-IMS analysis of 2 hour kidney tissue illustrated that carboxy-dabrafenib was localized to the medulla, while desmethyl-dabrafenib was predominantly in the cortex, possibly a reflection of the differences in polarity between carboxy-dabrafenib (hydrophilic) and desmethyl-dabrafenib (lipophilic). The levels of dabrafenib, carboxy-dabrafenib and hydroxy-dabrafenib in xenograft tumor homogenate were consistently lower than those in plasma, whereas levels of desmethyl-dabrafenib were higher in xenograft tumor than in plasma, although its formation upon sample processing could not be ruled out. Dabrafenib, hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib were detected in plasma, but only dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib were detected in brain tissue homogenate (including CSF). The brain/plasma AUC_{0-t} ratios for dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib were 0.02, 0.009 and 0.3, respectively, based on total concentrations or 4.25, 0.14 and 36 after correcting for protein binding, suggesting that after repeat dosing, desmethyl-dabrafenib and to a lesser extent dabrafenib may penetrate intact brain tissue. This is consistent with the positive PD activity observed in the mouse brain tissue as assessed by changes in pERK/tERK levels following repeat dosing.

In a single dose quantitative whole body autoradiography (QWBA) study in partially pigmented rats, ^{14}C-dabrafenib-associated radioactivity was widely distributed into tissues, and most tissue concentrations were lower than those observed in blood. In blood and most tissues, the highest concentration of radioactivity was observed at 4 hours post dose. Radioactivity in the brain was below the limit of quantification (BLQ) at all time points, and there was no selective association of radioactivity with melanin containing tissues. By 3 days post dose the radioactivity in most tissues was BLQ, with the exception of the adrenal cortex, kidney and liver which were all BLQ at 35 days.

In a positron emission tomography study in the pig, after a single dose of ^{18}F-dabrafenib, consistent with the results in the rat, there was no evidence for brain penetration of drug-related material (DRM), including the circulating metabolites (hydroxy-dabrafenib and carboxy-dabrafenib) which were detected in this study.

In vitro, dabrafenib was highly bound to plasma proteins (≥98.4%) in mouse, rat, dog, monkey and human, and had minimal association with blood cells (blood to plasma concentration ratios ranged from 0.49 to 0.63). A similar blood:plasma ratio was found in vivo in. Dabrafenib was stable in the blood after a 2 hour incubation at 37°C. Hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib were all highly bound to plasma proteins (≥94.9%, ≥93.3% and ≥99.2%, respectively) in all species tested and had minimal association with blood cells (blood to plasma concentration ratios ranged from 0.45 to 0.71). In human plasma, dabrafenib, hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib were 99.7, 96.3, 99.5 and 99.9% bound to plasma proteins, respectively. The blood to plasma concentration ratio for dabrafenib in human was 0.54.

In vitro, dabrafenib, hydroxy-dabrafenib and desmethyl-dabrafenib were substrates of human P-glycoprotein (Pgp) while carboxy-dabrafenib was not. Dabrafenib (only compound tested) was a substrate of murine breast cancer resistance protein 1 (Bcrp1) *in vitro* and showed high intrinsic apparent permeability (415 nm/sec in Bcrp-MDCK cells).

The *in vitro* permeability of dabrafenib at pH 7.4 and 5.5 exceeded that of the high permeability reference marker labetalol. Therefore, dabrafenib is classified as a highly permeable compound, according to the Biopharmaceutics Classification System.

The metabolism of 20 µM [^{14}C]-dabrafenib was investigated in studies *in vitro* using hepatocytes from male mice, rats, dogs, and monkeys, female rabbits, and male and female humans. While most metabolites observed in human hepatocytes were also observed in at least one preclinical species, four conjugated metabolites were not. There were also some minor differences between hepatocytes from different human beings with respect to these conjugated metabolites. With the exception of desmethyl-dabrafenib, which was not detected in dog hepatocytes, the main metabolites hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib were detected in all species. Direct glucuronidation of dabrafenib was observed in rat, dog and rabbit. Many preclinical species also exhibited unique metabolites not observed in hepatocytes from any other species. Monkey hepatocytes contained six, and dog produced two unique products of oxidation or oxidation/glucuronidation. Rabbit hepatocytes contained two unique metabolites (products of oxidation and oxidation with sulfation), while rat exhibited a product of oxidation, defluorination, and glutathione conjugation not observed in any other species.

In *vitro* studies using cDNA expressed enzymes and human liver microsomes with specific CYP inhibitors showed that dabrafenib was metabolized to hydroxy-dabrafenib mainly by CYP2C8 and CYP3A4, while hydroxy- and desmethyl-dabrafenib were further oxidized mainly by CYP3A4.

In vivo, single oral dose metabolism studies were conducted using [14C] dabrafenib in female nude mice (30 mg/kg), intact male and female rats and male bile duct cannulated rats (10 mg/kg), and male and female dogs (10 mg/kg). The metabolic profiles obtained for dabrafenib in circulation were qualitatively similar in all species studied, in that the majority of the drug-related material was present as dabrafenib and 3 pharmacologically active metabolites, hydroxy dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib. At 2 hours following a single dose of [14C]-dabrafenib, carboxy-dabrafenib was the major component in mouse plasma. This represented more than 50 % of plasma radioactivity from 2 hours post-dose, with C_{max} of 4.5 µg/ml and AUC of 34 µg.h/ml. Hydroxy-dabrafenib, desmethyl-dabrafenib, and dabrafenib were detected through 12 hours post-dose.

In rats, hydroxy-dabrafenib was the predominant radiolabelled component in plasma, accounting for 50-80 % of plasma radioactivity at all time points studied. In addition, dabrafenib and carboxy-dabrafenib were present, while desmethyl-dabrafenib was a minor plasma component (<5% of plasma radioactivity). Rat liver extracts showed similar profiles to those in plasma, except that desmethyl-dabrafenib was not observed in liver.

In dogs, the predominant radiolabelled component in plasma was dabrafenib, while hydroxy-dabrafenib was a notable component (>10 %). Carboxy-dabrafenib and desmethyl-dabrafenib were minor components of dog plasma only observed at later time points.

Following a single dose of [14C]-dabrafenib in humans, dabrafenib was the major component in human plasma at 2 hours, and by 10 hours post dose carboxy-dabrafenib was the major drug-related component in human plasma.

The excretion balance of 14C-dabrafenib was investigated in rats and dogs. In intact rats, fecal excretion was the major route of elimination, accounting for means of 92.9% and 90.2% of the administered dose in males and females, respectively; mean urinary elimination accounted for <3.1% of the dose. Fecal excretion was the predominant route of elimination of 14C-dabrafenib-related material in dogs, accounting for mean recoveries of 101% and 103% of the dose in males and females, respectively; urinary excretion accounted for means of <1% of the dose in both genders.

2.3.4. Toxicology

Single dose toxicity

The single-dose toxicity of dabrafenib was examined in rats and dogs. Results of single-dose toxicity studies are summarised in the following table.

Table 05 Single-dose toxicity studies performed with dabrafenib

Study ID / GLP-status	Species / Sex / Number / Group	Dose / Route	Observed max non-lethal dose	Major findings
CD2009/00799/00/ Non-GLP	Crl:CD (SD) Rat 3M,3F	20, 200, 400, 600 oral gavage*	600 mg/kg	Dose-related body weight loss was noted at all dose levels on day 2.

CD2008/00850/00/ Non-GLP	Beagle dogs 1M,1F	30, 100 , 300, 600 oral gavage	600 mg/kg	Body weight loss occurred for all dogs. Reduced food intake and abnormal faecal consistency at all doses. Emesis at doses ≤ 300 mg/kg.
CD2009/00563/00/ Non-GLP	Beagle dogs 2M,2F	2.5, 20, 40, 80, 20 twice daily, oral capsules*	80 mg/kg	Females lost body weight at all doses that contained Avicel, with the exception of the 20 mg/kg twice daily dose. Vomiting following doses of 20 mg/kg twice daily with Avicel and 80 mg/kg without Avicel.

*****dabrafenib mesylate

Repeat dose toxicity

The toxicity of repeated oral gavage doses of dabrafenib has been assessed in rats (at doses up to 200 mg/kg/day for up to 13 weeks), dogs (doses up to 50 mg/kg/day for 4 weeks; doses up to 20 mg/kg/day for 13 weeks) and in mice (doses up to 1000 mg/kg/day for 2 weeks). Results of single-dose toxicity studies are summarised in table 6.

Table 06 Repeat-dose toxicity studies (pivotal) performed with dabrafenib

Study ID **Species/Sex/ Duration/** **Number/Group**	**Dose** **(mg/kg/day)**	**Major findings**
2010N109898_00 **Mouse** **14 days** 10M /10F	0,100, 300 1000, QD	Minimal spermatid retention in the seminiferous tubulues in majority of males at all doses. Increased incidence of prominent residual bodies in the seminiferous tubules of males at ≥300 mg/kg. Lower thymus weight in males, most prominent at 300 mg/kg with lower lymphocyte count. Higher total white blood cells in females at 100 mg/kg.

CD2008/01511/02 **Rat** **4 weeks** + 2 weeks recovery C+HD 10+6M /10+6F	0,5,20,200,QD	Minimal to mild bilateral degeneration of elongated spermatids with spermatid retention at all doses. Minimal to mild cellular debris in epididymides at all doses. Testes and epididymal changes did not recover. Body weight loss and reduced food consumption in HD rats. Minimal to mild focal epithelial (keratinocyte) degeneration in the keratin overlaying the junctional ridge of the stomach at all doses (reversed after recovery). Slight dose-related increase in incidence of minimal cardiomyopathy in males at ≥20 mg/kg.
CD2010/00052/00 **Rat** **13 weeks** + 4 weeks recovery C+MD+HD 12+6M/12+6F	0,20,200,400, QD	Minimal to marked cutaneous acanthosis/hyperkeratosis, with corresponding macroscopic changes, affected the footpads and interdigital skin of paws (all doses). Minimal to marked hyperplasia of the non-glandular gastric mucosa at all doses. Minimal to moderate down-growth of the hyperplastic epithelium into the submucosal muscularis mucosa in females at ≥200 mg/kg and males at all doses. Epithelial findings showed partial recovery. Minimal to severe seminiferous tubular degeneration/depletion with secondary epidyimal oligo/aspermia in males at all doses with corresponding decreased testes weights at ≥200 mg/kg. A clear dose response in overall severity. Testicular/epidydimal changes present in most males after recovery. Minimal to slight midzonal hepatocellular vacuolation in a few animals at ≥200 mg/kg. Increases in lymphocyte, eosinophil, neutrophil and monocyte counts which were resolved after recovery.
CD2008/01503/02 **Dog** **4 weeks** + 2 weeks recovery C+HD 3+2M/3+2F	0,1,5,50,QD	Marked hypertrophy and mild focal hemorrhage of the tricupspid (right atrioventricular valve) in one male at 50 mg/kg.Raised, depigmented areas on skin and/or a pedunculated mass (ears, lips, chin, slight to extreme in severity) in one control dog and 4 dogs at 50 mg/kg observed clinically during weeks 3-4. These changes were not evident clinically or macroscopically after 2 weeks recovery.
CD2010/00051/00 **Dog** **13 weeks** + 4 weeks recovery C+HD	0,5,20,60 (M) 100 (F),BID	Due to severity of clinical signs and body weight loss, dosing of animals given 60/100 mg/kg was discontinued after 14/15 days. Animals exhibited thin body condition, inappetance, body weight loss, dehydration, red gums/gingivitis, liquid feces and emesis. Main study animals were euthanized on days 22/23 after 1 week off-dose, recovery animals were euthanized on days 46/47 after 4 weeks

4+3M/4+3F		off-dose.Administration of dabrafenib at 60/100 mg/kg/day over 14/15 days was associated with microscopic findings in the lung (slight lobar bronchoalveolar inflammation), sternal bone marrow (minimal to slight myeloid hypercellularity), thymus (moderate to marked lymphoid depletion), testis (minimal to slight degeneration/depletion of the seminiferous epithelium), epididymis (slight oligo/aspermia; minimal to slight intratubular cellular debris), liver (minimal to moderate hepatocellular vacuolation) and oral cavity (moderate bilateral gingival inflammation, erosion/ulceration, with underlying bone resorption and osteomyelitis, observed in a female given 100 mg/kg/day). Findings observed in sternal bone marrow, thymus, liver, lung and oral cavity were not seen in dogs euthanized after the 4 week recovery period. However, changes in the testis and epididymis were still present in several males. In addition, cardiac fibrovascular proliferation was observed in the right atrium of a male after the recovery period without any apparent physiological change as electrocardiographic (ECG) and echocardiographic findings were within normal limits. 20 mg/kg/day: Body weight loss, skin lesions (papules, red skin, skin scabs) at several site, swollen paws and ear discharge. Increases in neutrophil and monocyte counts. Increases in serum alkaline phosphatase. Decreases in urea, creatinine, albumin, cholesterol, phosphorus and potassium. Marked fibrovascular proliferation in the heart (1F). Marked acanthosis/hyperkeratois, mixed cell infiltration and erosion/crust in skin. Minimal to slight myeloid hypercellularity in sterna bone marrow. Slight to marked lymphoid depletion in thymus. Minimal to moderate degeneration/depletion of the seminiferous epithelium in testes. Slight to sever oligo/aspermia in epididymis. Slight to marked lobar bronchoalveolar inflammation in lung. Minimal to slight plasmacytosis and erythrocytosis/erythrophagocytosis in popliteal lymph nodes.Similar histological changes were noted in dogs given 5 mg/kg/da but were limited to skin, testes, epididymis and popliteal lymph nodes and were generally of lower severity.

Genotoxicity

Dabrafenib has been evaluated for genotoxic potential *in vitro* and in *vivo*. The mutagenic potential of dabrafenib has been assessed in the standard Ames test and in mammalian cells in the mouse lymphoma assay. The *in vivo* clastogenic potential of orally administered dabrafenib has been assessed in rats using the micronucleus test. In all studies, dabrafenib was not mutagenic in either *in vitro* or *in vivo* test systems (data not shown).

Carcinogenicity

No studies were submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

An overview of the reproductive and developmental toxicity studies is presented in Table 7. The pivotal juvenile toxicity study which was ongoing at the time of submission, was performed as part of the Paediatric Investigation Plan agreed upon by the EMA in January 2012.

Table 07 Reproductive and developmental toxicity studies with dabrafenib

Study type / Study ID / GLP	Species; Number / group	Dose (mg/kg/day) and dosing period	Major findings
Preliminary female fertility, early embryonic and embryofetal development 2010N107959_00 Non-GLP	Rat 7F	0, 5, 20, 200 5 weeks starting 14 days prior to co-habition, for up to 4 days of co-habitation and on days 0 to 17 post coitum	At 200 mg/kg body weight loss during days 1-14. At 20 mg/kg reduced body weight gain days 1-14. No effect at any dose on body weight between days 0 – 17 pc. No effects on estrous cycle, mating or fertility. No effect on numbers of corpora lutea, post-implantation resorptions or live and dead foetuses per litter, gravid uterine weight or placental morphology. Increase in percentage of pre-implantation loss (4.7%, 4.8%, 15.2%, 11.1% in the respective dose groups). Non-dose-dependent decrease in fetal body weight (5-7%). No external or visceral malformations. Increase incidence of variations in the shape of the thymus at 200 mg//kg (4/81 fetuses in 2/6 litters – control 0/93, 7 litters).
Female fertility, early embryonic and embryofetal development 2011N113146_00 GLP	Rat 25F	0, 5, 20, 300 5 weeks starting 15 days prior to co-habition, during co-habitation (up to 14 days if needed) and on days 0 to 17 post coitum	One female at 300 mg/kg euthanized on day 6 of study due to lethargy, splayed hindlimbs, dehydration, hyperactivity and large body weight loss. At 300 mg/kg body weight loss during cohabitation At ≥20 mg/kg reduced body weight gain between days 0-18 pc. Decrease in number of corpora lutea (14.0 vs 15.9) and corresponding decrease in number of implantations (13.2 vs 15.0) at 300 mg/kg. Increase in percentage post-implantation loss, primarily due to early resorptions at 300 mg/kg (12.4 vs 4.2). Significant decrease in number of live foetuses per litter at 300 mg/kg (11.6 vs

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<td>14.9).
No effect on estrous cycle, mating, fertility, sex ratio, placental morphology.
At ≥20 mg/kg decrease in fetal body weight and a corresponding decrease in gravid uterine weight.
At 300 mg/kg 3 fetuses with cardiac ventricular septal defects (none in control).
At ≥20 mg/kg variations of the thymus (split or variation in shape) (20 mg/kg: 5 fetuses; 300 mg/kg: 4 fetuses). Increase incidence of fetal variations of delayed skeletal development at ≥20 mg/kg.
Toxicokinetics:
<table>
<tr><th>Dose (mg/kg)</th><th>Cmax (µg/ml)</th><th>AUC (µg•h/ml)</th><th>exposure multiple Cmax</th><th>expos e multi AUC</th></tr>
<tr><td>5</td><td>0.765</td><td>2.62</td><td>0.5</td><td>0.3</td></tr>
<tr><td>20</td><td>1.17</td><td>4.10</td><td>0.8</td><td>0.5</td></tr>
<tr><td>300</td><td>2.17</td><td>22.6</td><td>1.4</td><td>2.6</td></tr>
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<tr>
<td>Preliminary juvenile toxicity
2011N121500_01
Non-GLP</td>
<td>Rat
Up to 6M/6F</td>
<td>Doses from 1 to 1000 mg/kg with various dose escalation protocols
Post-natal day 7 to 35.</td>
<td>Endpoints in this study included clinical observations and macroscopic observations; no clinical chemistry, haematology or histopathology was performed. Findings on decreased skin turgor and thin hair coat were common, and there were mortalities related to treatment.</td>
</tr>
</table>

Toxicokinetic data

Comparison of mean systemic exposure of principal circulating metabolites in plasma across species following repeat dose administration of dabrafenib (highest tolerated doses) is presented in Table 8.

Table 08 Mean systemic exposure of circulating dabrafenib metabolites in plasma across species.

Study Type Report No. (Study No.)	Highest Tolerated Dose (mg/kg/day)	Sex	Animal to Human Ratio Carboxy-Dabrafenib[a,b]		Animal to Human Ratio Hydroxy-Dabrafenib[a,b]		Animal to Human Ratio Desmethyl-Dabrafenib[a,b]	
			C_{max}	AUC	C_{max}	AUC	C_{max}	AUC
Mouse 14 day 2010N109898_00 (M29485)	1000	M F	7.1 5.7	3.3 2.8	1.6 2.6	0.9 1.9	42.0 24.8	13.9 9.9
Rat 13 week CD2010/00052/00 (G08219)	200	M F	0.45 0.76	0.49 0.54	2.7 8.4	4.3 7.1	0.30 0.35	0.25 0.21
Dog 4 week combination[c,d] 2011N112335_00 (G10260)	20	M F	0.02 0.02	0.03 0.02	1.8 1.7	3.9 3.1	0.23 0.17	0.22 0.14
Dog 13 week[c] CD2010/00051/00 (G09131)	20	M F	0.04 0.05	0.04 0.05	1.6 2.7	2.8 4.5	0.46 0.65	0.28 0.38
Human[a]	300 mg/day	M&F	6.1	103	1	8.1	0.35	6.1

Key:
a = Estimated mean AUC_{0-24} values based on actual geometric mean AUC_{0-12} values of 51.48, 4.07 and 3.07 µg.h/mL for carboxy-dabrafenib, hydroxy-dabrafenib and desmethyl-dabrafenib metabolites, respectively, achieved in subjects given 150 mg BID (TDD 300 mg HPMC capsules) on Week 6 [Phase III Study BRF113683].
b = Calculated for C_{max} and AUC based on end of treatment values for animal studies.
c = Study conducted using dabrafenib mesylate.
d = Dabrafenib in combination with trametinib (GSK1120212, a MEK kinase inhibitor).
– = No data; only toxicokinetic data for dabrafenib and hydroxy-dabrafenib were evaluated in 4 week rat and dog studies.

Local Tolerance

The intended route of dabrafenib administration in patients with unresectable or metastatic melanoma with a BRAF V600 mutation is oral. Local tolerance studies have been performed with dabrafenib drug substance for worker health and safety purposes only (data not shown).

Other toxicity studies

Phototoxicity

In a neutral red uptake phototoxicity test, Balb/c 3T3 mouse fibroblasts cells treated with dabrafenib mesylate (micronized, 0.316 to 316 µg/mL) both in the presence and absence of UV-A light resulted in a decrease in cell survival. Cytotoxicity was observed at the highest three concentrations analyzed in the absence of UV-A (31.6 to 316 µg/mL) and all concentrations analyzed in the presence of UV-A (0.316 to 316 µg/mL). The IC50 value of dabrafenib in the absence of UV-A was 26.076 µg/mL. However, in the presence of UV-A, the IC50 value of dabrafenib could not be reliably calculated and is thus <0.316 µg/mL (the lowest concentration evaluated in the assay). The PIF (photo irritation factor) value was >83, indicating the test article was phototoxic.

2.3.5. Ecotoxicity / environmental risk assessment

Summary of main study results

Substance (INN / Invented Name): Dabrafenib			
CAS-number: 1195768-06-9			
PBT screening		**Result**	**Conclusion**
Bioaccumulation potential GLP		log D_{ow} 3.229 at pH=5 3.384 at pH=7 0.168 at pH=9	Potential PBT: Potential for bioaccumulation
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$ Default Fpen =0.01 PEC $_{surfacewater}$ Default Fpen replaced with melanoma prevalence data for the European Union, estimated based on the complete prevalence proportion for Nordic countries (0.24%).	1.5 0.36	µg/L	> 0.01 threshold: Yes
Other concerns (e.g. chemical class)			No
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption GLP	OOPTS 835.1110, using one type of sludge at concentrations in the range 1-12 g/L.	K_{oc} =2460	Low binding to sludge.
Inherent ultimate biodegradability test GLP	OECD301B/302C	Not readily or inherently biodegradable. Ultimate biodegradation (DOC)=0% at day 28 Primary degradation= 63% on day 14 and 81% at day 28.	Results suggest primary degradation of parent compound in the STP's, but low ultimate biodegradation.
Aerobic and anaerobic Transformation in Aquatic Sediment systems GLP	OECD 308 Two water-sediment systems over a period of 100 days.	$DT_{50, water}$ =16-28 days $DT_{50, sediment}$ = No detectable decline over the study period (100 days) $DT_{50, whole\ system}$ = 162-307 days (extrapolated) % shifting to sediment =96-100%	Results show dissipation from water surface into sediment where dabrafenib appears to be persistent. This triggers a sediment toxicity test. Formation of metabolites was detected in both water and sediment portions.
Phase IIa Effect studies			

Study type	Test protocol	Endpoint	Value	Unit	Remarks
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata* GLP	OECD 201	NOEC	0.22	mg/L	72 hours
Daphnia sp. Reproduction Test/ *Daphnia magna* GLP	OECD 211	NOEC	0.105	mg/L	21 days
Fish, Early Life Stage Toxicity Test/*Pimephales promelas* GLP	OECD 210	NOEC	1.47(length) 2.61 (wet weight) 3.65 (hatching success and post-hatch survival	mg/L	21 days
Activated Sludge, Respiration Inhibition Test GLP	OECD 209	Total respiration EC_{50} NOEC	>1000 312.5	mg/L	
Phase IIb Studies					
Bioaccumulation *Onchorhynchus mykiss* GLP	OECD 305	BCF	**0.01 mg/L** BCF_{ss}=4.38 Depuration DT_{50}=0.71 days DT_{95}=3.06 days **0.1 mg/L** BCF_{ss}=4.38 Depuration DT_{50}=0.71 days DT_{95}=3.06 days	L/kg	28 days exposure 13 days depuration Due to low uptake of radioactive residues, lipid values were not used in BCF calculation. BCF < 5 suggest low potential for bioaccumulation. TGD B criterion: BCF > 2000
Sediment dwelling organism *Chironomus riparius* GLP	OECD 218 Nominal test concentrations up to 1000 mg/kg	NOEC	Emergence success: 64 Development rate:160 Sex ratio: 160	mg/kg as free base	Toxicity on the sediment-dwelling non-biting midge, *Chironomus riparius* was detected at concentrations >64 mg/kg.

Phase IIa risk evaluation

Calculations of PNEC based on results from studies conducted in phase IIa studies using assessment factors are summarised below.

	NOEC	AF	PNEC
$PNEC_{surfacewater}$	0.105 mg/L *(Daphnia magna)*	10	0.0105 mg/L
$PNEC_{groundwater}$	0.105 mg/L *(Daphnia magna)*	10	0.0105 mg/L
$PNEC_{microorganism}$	312.5 mg/L (sludge inhibition)	10	31.25 mg/L

$PEC_{groundwater}$

$PEC_{groundwater}$ = 0.25 x $PEC_{surfacewater}$ = 0.25 x 0.36 µg/L = 0.09 µg/L

Environmental compartment	PEC	PNEC	PEC/PNEC	Trigger value	Conclusion
Surfacewater	0.36 µg/L	10.5 µg/L	0.034	1	No risk
Groundwater	0.09 µg/L	10.5 µg/L	0.009	1	No risk
Sewage water	0.36 µg/L	31250 µg/L	1.2×10^{-5}	0.1	No risk

Phase IIb risk evaluation

Dabrafenib has an adverse effect on the emergence success of *Chironomus riparius* at concentrations >64 mg/kg in a sediment toxicity test (OECD 218). PEC sediment has been calculated according to equations in REACH guidance and TGD.

$PEC_{sediment}$ based on a $PEC_{surface\ water}$ = 0.36 µg/L (Estimated melanoma prevalence data, Fpen=0.24%)

$PEC_{sediment} = K_{susp\text{-}water}/RHO_{susp} * PEC_{local\ water} * 1000$

Where:

Ksusp-water = Water suspended matter - water partitioning coefficient = 61.5 $[m^3.m^{-3}]$

RHOsusp = Bulk density of suspended matter $[kg.m^{-3}]$ = 1150 kg/m^3

$PEC_{sediment}$ = 246/1150 * 0.36 * 1000 = 77.01 µg/kg

$PNEC_{sediment}$

$PNEC_{sediment}$ is calculated based on the NOEC value in the study on *Chironomus riparius*, applying an assessment factor of 100.
$PNEC_{sediment}$ = 64000 µg/L / 100 = 640 µg/L

Environmental compartment	PEC (µg/kg)	PNEC (µg/L)	PEC/PNEC	Trigger value	Conclusion
Sediment	77.01	640	0.120	1	No risk

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation to be addressed:

The MAH should perform an OECD 106 adsorption study for soils for dabrafenib and submit the results of this study with accompanying reports and a revised environmental risk assessment (with recalculated PEC for sediment and the RQ).

Discussion on non-clinical aspects

Dabrafenib is a selective inhibitor of human RAF kinases with activity against WT CRAF, BRAF and BRAFV600E/D/K. Dabrafenib showed similar activity with BRAF from human, rat, dog and cynomolgus monkey. Oral doses of dabrafenib produced significant tumour growth inhibition in mice bearing BRAFV600E mutant human tumour xenografts.

In biochemical assays, dabrafenib showed a higher affinity for the mutated BRAF variants (V600E, V600D, V600K) as compared to wildtype BRAF. However, the difference is relatively small (<8-fold). The activity against tumours with mutated BRAF is not due to this slightly higher activity but due to the fact that the mutations lead to constitutive activation of the enzyme and the tumour growth will be highly dependent on this activity. In tumours with wildtype BRAF, the enzyme does not play such essential role. It was also clear from the presented data that tumour cells with mutated BRAF may become resistant to dabrafenib due to the presence of mutations in other kinases such as MEK1 and MEK2.

The most common activating mutation in BRAF is the V600E (valine to glutamic acid) which has been clearly shown to be associated with sensitivity to dabrafenib. Other activating mutations, which occur less common, are the V600K and V600D. The applicant presented data on several cell lines carrying the V600K which are sensitive to dabrafenib, but only one cell line with V600D (WM115) was also sensitive to dabrafenib. From a pharmacological viewpoint it could be considered that tumours with V600E, V600K and V600D are equally sensitive to dabrafenib due to the similar enzyme inhibition and the fact that all mutations are associated with constitutive activation of BRAF.

There were no dabrafenib-related acute neurobehavioral or respiratory effects in rats given single oral doses up to 200 mg/kg/day. Cardiovascular effects were observed in two species (increased heart rate in rat and dog and decrease in PR interval duration in dog). These findings should be taken into consideration when discussing the overall cardiovascular safey of the product (see Toxicology section). Inibition of hERG was observed at high concentrations with large multiples to clinical exposure and there were no arrhythmic effects in the dog. No toxicokinetics was performed in the dog cardiovascular study. Estimation of exposure in the dog cardiovascular safety study was done from toxicokinetics data in a 4 week study. These data show that exposures up to 5x clinical exposure were achieved in absence of ECG abnormalities

Regarding pharmacokinetics the applicant has presented appropriate data on absorption in animal species. Bioavailabiliy was high in all species. *In vitro*, dabrafenib and its metabolites hydroxy-, carboxy- and desmethyl-dabrafenib were highly bound to plasma proteins in nonclinical species and humans. The main human metabolites, hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib, are found in nonclinical species, however with quantitative differences. Exposure margins in repeat dose toxicity studies were determined and are discussed further below. Excretion in urine is clearly higher in humans (23%) than in toxicology species (≤ 3.1%). The main metabolite in urine is carboxy-dabrafenib which shows some pharmacological activity. There is a theoretical possibility for toxicity to the kidney and the urinary tract due to the urinary excretion, which was observed in the toxicology studies (see discussion below).

Cardiovascular pathology has been observed on toxicology studies ranging from 7 days to 13 weeks duration in rats and dogs over a broad range of exposures. The same structural findings were not observed in subsequent studies of longer duration, but cardiovascular pathology was consistently observed. In dogs, the findings were principally characterized by coronary arterial degeneration/necrosis and/or haemorrhage, cardiac atrioventricular valve hypertrophy/haemorrhage and atrial fibrovascular proliferation (≥ 2 times clinical exposure based on AUC). In rats, an increased incidence of hepatic arterial degeneration and spontaneous cardiomyocyte degeneration with inflammation (spontaneous cardiomyopathy) were observed (≥ 0.5 times clinical exposure). Bronchoalveolar inflammation of the lungs was observed in several dogs at ≥ 20 mg/kg/day (≥ 9 times human clinical exposure based on AUC) and was associated with shallow and/or laboured breathing.

In repeat dose studies, mild to marked reversible decreases in reticulocyte counts and decreased red cell mass was noted in dogs. In rats, decreased red cell mass were observed in female rats without corresponding microscopic findings in the bone marrow. Minimal to marked lymphoid depletion with reduced thymus weights were observed in dogs.

Carcinogenicity studies with dabrafenib have not been conducted and are not considered necessary to support the use of dabrafenib for the current indication (BRAF V600 mutant positive advanced or metastatic melanoma) with short life expectancy. Dabrafenib was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay.

In combined female fertility, early embryonic and embryofetal development studies in rats numbers of ovarian corpora lutea were reduced in pregnant females at 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC), but there were no effects on estrous cycle, mating or fertility indices. Developmental toxicity including embryo-lethality and ventricular septal defects were seen at 300 mg/kg/day, and delayed skeletal development and reduced fetal body weight at ≥ 20 mg/kg/day (≥ 0.5 times human clinical exposure based on AUC). Male fertility studies with dabrafenib have not been conducted. However, in repeat dose studies, testicular degeneration/depletion was seen in rats and dogs (≥ 0.2 times the human clinical exposure based on AUC). Testicular changes in rat and dog were still present following a 4-week recovery period. Dabrafenib should not be administered to pregnant women unless the potential benefit to the mother outweighs the possible risk to the foetus. If the patient becomes pregnant while taking dabrafenib, the patient should be informed of the potential hazard to the foetus.

In a juvenile toxicity study in rats, effects on growth, renal toxicity, testicular toxicity and earlier vaginal opening were observed. Juvenile rats showed higher levels of carboxy-dabrafenib. These data are compatible with the possibility that renal clearance of this metabolite is associated with renal toxicity, and that this potential toxicity would not be readily detected in adult animals. Renal toxicity has been observed clinically and the SmPC includes information on it. No further nonclinical investigations are warranted to study the potential renal toxicity of carboxy- dabrafenib.

Dabrafenib was phototoxic in an *in vitro* mouse fibroblast 3T3 Neutral Red Uptake (NRU) assay. The nonclinical photoxicity findings are mentioned in the SmPC.

Dabrafenib is not expected to pose a risk to the environment. However the CHMP concluded that the MAH should perform an OECD 106 adsorption study for soils for dabrafenib and submit the results of this study with accompanying reports and a revised environmental risk assessment (with recalculated PEC for sediment and the RQ).

2.3.6. Conclusion on the non-clinical aspects

The non-clinical studies submitted for the marketing authorisation application for dabrafenib were considered adequate and acceptable for the assessment of non-clinical aspects for the product dabrafenib.

2.4. Clinical aspects

2.4.1. Introduction

The Applicant applied for the indication ''Dabrafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation''.

The recommended dose of dabrafenib is 150 mg (two 75 mg capsules) twice daily (corresponding to a total daily dose of 300 mg). Dabrafenib should be taken at least one hour before, or at least 2 hours after a meal, leaving an interval of approximately 12 hours between doses. Dabrafenib should be taken at similar times every day to increase patient compliance.

The Applicant received Scientific Advice from the CHMP on clinical efficacy and safety related to the pivotal study BREAK-3. In the Scientific Advice procedure the CHMP concurred that the proposed study design, target population, primary endpoint and the safety database would be adequate to support a Marketing Authorisation Application. Regarding the selected dose the CHMP considered that the proposed dose could be considered acceptable however it was recommended that it might be relevant to consider evaluating the highest tolerable dose.

GCP

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

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

- Tabular overview of clinical studies

Table 09 Development Program for Dabrafenib as Monotherapy in Metastatic Melanoma

Study Identifier	Protocol Name	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	BRAF Mutation Status at Enrollment [b]	Total No. of Subjects by Group Entered/ Completed
BREAK-3 (BRF113683)	A Phase III randomized, open-label study comparing dabrafenib to DTIC in previously untreated subjects with BRAF mutation positive metastatic melanoma	Dabrafenib (HPMC) 150 mg BID (dose may be reduced); oral; DTIC 1000 mg/m² every 3 weeks; continued treatment until disease progression, death or unacceptable adverse event	V600E: 249 V600K: 1[a]	Dabrafenib 187 enrolled 80 completed DTIC 63 enrolled 46 completed
BREAK-MB (BRF113929)	A Phase II open-label, two-cohort, multicenter study of dabrafenib as a single agent in treatment naïve and previously treated subjects with BRAF mutation-positive metastatic melanoma to the brain	Dabrafenib (HPMC) 150 mg BID (dose may be reduced); oral; continued treatment until disease progression, death or unacceptable adverse event	V600E: 139 (Cohort A: 74; Cohort B: 65) V600K: 33 (Cohort A: 15; Cohort B: 18)	172 Enrolled Cohort A: 89 enrolled 63 completed Cohort B: 83 enrolled 56 completed
BREAK-2 (BRF113710)	A Phase II single-arm, open-label study of dabrafenib in BRAF mutant metastatic melanoma	Dabrafenib (Gelatin) 150 mg BID (dose may be reduced); oral; continued treatment until disease progression, death or unacceptable adverse event	V600E: 76 V600K: 16	92 enrolled/ 59 completed

a. Randomized in error and did not receive treatment; included in ITT population but not the Safety Population
b. An allele-specific real-time PCR assay was utilized to specifically detect the BRAF V600E vs. V600K mutation.

2.4.2. Pharmacokinetics

A total of 9 clinical studies with pharmacokinetic (PK) data were submitted (Table 10), with 766 subjects receiving dabrafenib, including five studies in patients with BRAF mutant solid tumours (BRF113463, BRF113479, BRF113468, BRF112680, BRF113771), and five studies in patients with BRAF mutation-positive melanoma (BRF112680, BRF113220, BRF113710, BRF113929, BRF113683). Both women and men were included in the studies, the majority (96 %) of the subjects were Caucasian.

Population pharmacokinetic analysis (2011N113667) and pharmacokinetic pharmacodynamic analysis (2011N120468) were made using data from four of the studies (BRF112680, BRF113710, BRF113929 and BRF113683).

Table 10 Clinical studies to support the Clinical Pharmacology evaluation of dabrafenib

Protocol	Type of Study	Formulation
BRF112680	FTIH (Single and Repeat Dose PK)	Gelatin Capsules
BRF113468	Food Effect/Particle Size (Relative Bioavailability)	Gelatin and HPMC Capsules
BRF113463	ADME (mass balance)	Suspension
BRF113479	Absolute Bioavailability	HPMC Capsules and IV solution
BRF113771	Drug Drug Interaction (DDI) and PK	HPMC Capsules
BRF113220	Combination with Trametinib	Gelatin Capsules[1]
BRF113710 (BREAK-II)	Phase II	Gelatin Capsules
BRF113929 (BREAK-MB)	Phase II (with brain metastases)	HPMC Capsules
BRF113683 (BREAK-III)	Phase III	HPMC Capsules

ADME: Absorption, distribution, metabolism and excretion

1. Data included in the interim report only includes PK data with gelatin capsules

The plasma concentrations of dabrafenib and its three metabolites, hydroxy-dabrafenib (M7), carboxy-dabrafenib (M4) and desmethyl-dabrafenib (M8) were determined using two different ultra high pressure liquid chromatography (UHPLC) methods coupled with tandem mass spectrometric (MS/MS) detection. In addition, a validated accelerator mass spectrometry (AMS) method was used to determine [14C] dabrafenib concentrations in plasma. As part of the clinical pharmacology DDI and drug combination studies, concentrations of midazolam, dexamethasone, and trametinib were assayed in plasma using validated methods. Concentrations of dabrafenib and its three metabolites were measured in urine for exploratory purposes.

Absorption

Dabrafenib mesylate is very slightly soluble at pH 1 and practically insoluble in the pH range 4-8 in aqueous media. Solubility in simulated gastric fluid (SGF, pH 1.2), fed state simulated intestinal fluid (FesSIF, pH 6.8) and fasted state simulated intestinal fluid (FasSIF, pH 6.2) was 43 µg/ml, 6.8 µg/ml and 6.2 µg/ml, respectively. Dabrafenib solubility is pH-dependent, with decreasing solubility at increasing pH.

Dabrafenib showed high *in vitro* permeability in Madin-Darby canine kidney (MDCKII) cells. Given the low solubility of dabrafenib, it may be classified as a BCS class II compound. Also the metabolites M7 and M8 were classified as high-permeability compounds while M4, which is more polar, showed low permeability.

Absolute oral bioavailability of dabrafenib at a single 150 mg dose from the commercial formulation (HPMC capsule) was shown to be around 95% (90 % CI: 81%, 110 %). Dabrafenib exposure (C_{max} and AUC) increased in a dose proportional manner between 12 and 300 mg following single-dose administration, but the increase was less than dose-proportional after repeat twice daily dosing. A decrease in exposure was observed with repeat dosing, likely due to induction of its own metabolism. Mean accumulation AUC Day 18/Day 1 ratios was 0.73. Following administration of 150 mg twice daily, geometric mean C_{max}, $AUC_{(0-\tau)}$ and predose concentration ($C\tau$) were 1478 ng/ml, 4341 ng*hr/ml and 26 ng/ml, respectively.

A preliminary evaluation of the effect of food on dabrafenib absorption after multiple doses was made in a subset of patients in study BRF112680. A moderate fat, moderate calorie meal showed no clinically meaningful changes in AUC following administration of repeat dose of dabrafenib gelatin capsules, with a mean ratio for AUCtau of 1.06 (90% CI: 0.668, 1.68). Cmax was lower when administered with food, with a mean ratio of 0.67 (90% CI: 0.40, 1.13).

The effect of a high-fat meal on the absorption of dabrafenib after a single dose of the commercial HPMC capsule was evaluated in Cohort 2 in study BRF113468. Fourteen (14) subjects randomly received two different treatments in a cross-over fashion: Regimen C where single dose of 150 mg dabrafenib as 2x75 mg HPMC capsule, dosed after a 10 hr fast (Subjects remained fasted for 4 hours after the dose) and regimen D where single dose of 150 mg dabrafenib as 2x75 mg HPMC capsule were taken within 30 minutes after start of eating a high-fat breakfast. Administration of dabrafenib HPMC capsules with a high-fat meal resulted in a mean 30% decrease in dabrafenib bioavailability (Cmax and AUC decreased by 51 % and 31 % respectively, relative to administration in a fasted state. Tmax was delayed from on average 2 hr to 6 hr, and t1/2 was prolonged from 8.4 hr to 10.6 hr.

Distribution

The human plasma protein binding of dabrafenib and its pharmacologically active metabolites at three different concentrations was determined *in vitro* in pooled human plasma from 3 male donors, using equilibrium dialysis. Plasma protein binding was determined to be 99.6%, 99.5% and 99.9% for dabrafenib, carboxy-dabrafenib (M4) and desmethyl-dabrafenib (M8) respectively and 96.3% for hydroxy-dabrafenib (M7). There was no evidence of concentration dependent protein binding.

Dabrafenib volume of distribution was estimated in the absolute bioavailability study, with an IV microdose of 50 µg [^{14}C]-dabrafenib administered together with a single oral 150 mg dose of un-labelled dabrafenib. Dabrafenib had a Vd_{ss} of 45.5 L, consistent with total body water. Vd_{ss} of the active metabolites was not determined.

Dabrafenib was determined to be a substrate for Pgp and BCRP *in vitro* and the active metabolites M7 and M8 were shown to be substrates for Pgp in adequately performed studies using monolayers of MDR1- or (murine) bcrp-transfected MDCKII cell lines, respectively. M4, which is more polar than dabrafenib, M7 and M8, was not a Pgp substrate.

Neither dabrafenib nor its 3 active metabolites were shown to be inhibitors of Pgp *in vitro*.

Metabolism

The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4 to form hydroxy-dabrafenib, which is further oxidized via CYP3A4 to form carboxy-dabrafenib. Carboxy-dabrafenib can be decarboxylated via a non-enzymatic process to form desmethyl-dabrafenib. Carboxy-dabrafenib is excreted in bile and urine. Desmethyl-dabrafenib may also be formed in the gut and reabsorbed. The geometric mean plasma half-life of dabrafenib, hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib was 8.4, 9.7, 20.9 and 22.2 hours respectively. Mean metabolite to parent AUC ratios following repeat-dose administration were 0.9, 11 and 0.7 for hydroxy-, carboxy-, and desmethyl-dabrafenib, respectively.

Elimination

The elimination of dabrafenib and its major metabolites has been characterised in a single dose mass-balance study and in several in vitro metabolism studies using human liver microsomes (HLM) and recombinant CYP enzymes. A total of 70% of the dose excreted in urine and faeces was structurally identified and quantified. In the mass-balance study (BRF113463) where four human subjects with BRAF mutation-positive solid tumours (3 M, 1 F) received a single oral dose of [^{14}C]-dabrafenib as an oral suspension (95 mg free base, 80 µCi) in the fasted state. Plasma and excreta were collected at various times or intervals through 240 hours postdose. Mean total recovery in the mass-balance study was 94%, with 71% and 23% of the dose recovered in faeces and urine respectively.

The geometric mean IV plasma clearance (CL) of dabrafenib was 12.0 L/hr. Terminal half-life following an intravenous single microdose is 2.6 hours. Dabrafenib terminal half-life after a single dose is 8 hours due to absorption-limited elimination after oral administration (flip-flop pharmacokinetics).

Dose proportionality and time dependencies

In a dose escalation study, pharmacokinetics of dabrafenib and its major metabolites were evaluated after single and repeated doses of 12 mg once daily (OD) up to 300 mg BID. This study was performed with the gelatin capsule.

Following the administration of 150 mg BID, the AUC was 47% lower on Day 15 relative to Day 1. Indeed, a 2-fold mean increase in the 6-β-hydroxycortisol-to-cortisol urinary ratio, a marker of CYP3A4 activity, was observed after repeat dosing, suggesting induction of CYP3A4 by dabrafenib.

Furthermore, dabrafenib exposure increased approximately linearly with dose after single doses, but less than dose-proportionally after repeated doses. On Day 15, a 2-fold increase in dose (150 mg BID vs. 300 mg BID) resulted in a 43% increase in dabrafenib $AUC_{(tau)}$ and no increase in C_{trough}. As dose dependency was observed at multiple doses but not at single doses, the dose dependency is likely due to dose-dependent auto-induction rather than to solubility-limited absorption.

Based on the population pharmacokinetic analysis, dabrafenib CL/F increases from about 12 L/hr after a single dose to about 35 L/hr at steady state. The time to steady state was estimated to be about 14 days and is dependent on half-life of the enzyme rather than half-life of dabrafenib and its metabolites.

The most potent metabolite, hydroxy-dabrafenib (M7), showed similar pharmacokinetics as dabrafenib, with about 47% lower exposure on Day 15 as compared with Day 1. Carboxy-dabrafenib (M4) and desmethyl-dabrafenib (M8) have longer half-lives than dabrafenib, and accumulated with repeat dosing, but less than dose-proportionally.

Due to the small increase in exposure at an increase in dose at the highest tested doses, a maximum tolerated dose (MTD) was not reached in the dose-escalation study as dose escalation was stopped at 300 mg BID.

Special populations

The effect of renal impairment on the pharmacokinetics of dabrafenib has not been investigated in a clinical study. In the population pharmacokinetic analysis, 233 (39.2%) subjects had mild (GFR 60-<90 mL/min/1.73 m^2) and 30 (5.0%) subjects had moderate (GFR <60 mL/min/1.73 m2) renal impairment. The effect of GFR on dabrafenib CL/F was small (<6% for both categories) and not clinically relevant. In addition, mild and moderate renal impairment did not have a significant effect on dabrafenib metabolite concentrations. No data are available in subjects with severe renal impairment.

The pharmacokinetics of dabrafenib has not been evaluated in subjects with hepatic impairment. In the population pharmacokinetic analysis, 65 (10.9%) subjects were categorized as having mild hepatic impairment, and since only 3 (0.5%) subjects had moderate hepatic impairment they were grouped together with subjects with mild impairment. There were no subjects with severe hepatic impairment in the data set. The oral clearance and thus exposure to dabrafenib was not significantly different between subjects with mild hepatic impairment and subjects with normal hepatic function (4% difference). In addition, mild hepatic impairment did not have a significant effect on dabrafenib metabolite concentrations.

In the population pharmacokinetic analysis weight was found to influence dabrafenib oral clearance (CL/F), oral volume of distribution (Vc/F) and apparent inter-compartmental clearance (Q/F). The predicted changes in exposure in a typical subject with low (50 kg) or high (140 kg) body weight as compared with a typical 80 kg subject was within 20% and thereby not considered clinically relevant. Body weight also affected the active metabolites M7 and M8 with <35% difference (inversely related relationship for M8) between each of the extremes and the typical value.

In the population pharmacokinetic analysis, there was no significant effect of age on CL/F of dabrafenib or M7, while age ≥75 years (n=21 subjects) was a significant predictor of M4 and M8 concentrations with a 41-42% greater exposure. Metabolite M8 is predicted to contribute less to the effect than dabrafenib and M7 (hydroxy-dabrafenib), respectively, and M4 (carboxy-dabrafenib) is suggested not to contribute.

No studies have been conducted to investigate the pharmacokinetics of dabrafenib in paediatric patients.

In the population pharmacokinetic analysis, dabrafenib CL/F was 9% lower (95% CI: 5%, 13%) in female subjects relative to male subjects, but this difference was not considered clinically meaningful. Sex had no significant influence on pharmacokinetics of the active metabolites.

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 was not explored.

Pharmacokinetic interaction studies

In study UH2008/00115/02 dabrafenib inhibited CYP1A2, 2C9, 2C19 and 2D6 with calculated IC50 values of >25, 10.9, 11, >25 µM, respectively. For CYP3A4, IC50s were 18.6 µM for testosterone and 15.6 µM for midazolam. In study CD2009/00012/00 dabrafenib inhibited CYP2C8 and 3A4 (atorvastatin, nifedipine) with calculated IC50 values of 8.2, 16 and 32 µM, respectively. Dabrafenib showed metabolism-dependent inhibition of CYP3A4 (nifedipine and midazolam) with 2.1 and 4.2 fold decrease in IC_{50} value. The control inhibitor, troleandomycin showed a 12- and 26-fold decrease in IC_{50} for nifedepine and midazolam respectively. In study 2010N110340 dabrafenib inhibited CYP1A2, 2C9, and 2C19 with calculated IC50 values of 87 µM, 7.2 µM, and, 22 µM, respectively.

In *vitro* studies performed with dabrafenib metabolites showed that M7 inhibited CYP1A2, 2C9 and 3A4 (midazolam) with calculated IC50 values of 83, 29 and 44 µM, respectively (Study 2010N111279). Metabolite M4 did not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 at concentration up to 100 µM and did not show any metabolism dependent inhibition of any of the tested CYP isoforms (Study 2010N110991-00). The third metabolite, desmethyl-dabrafenib (M8) inhibited CYP2B6, 2C8, C9, 2C19 and 3A4 (midazolam, atorvastatin, nifedipine) with calculated IC_{50} values of 78, 47, 6.3, 36, 17, 20 and 28 µM, respectively. For CYP3A4, desmethyl-dabrafenib showed metabolism-dependent inhibition with a decrease in IC_{50} value of 1.7 to 2.3 fold (Study 2010N1112910-01).

In study 2011N124750 the potential for increased exposure (AUC) of rosiglitazone (CYP2C8), warfarin (CYP2C9) or omeprazole (CYP2C19) if coadministered with dabrafenib, taking into account any contributing metabolites has been investigated. For dabrafenib the hepatic inlet concentration was estimated however, for the metabolites the unbound C_{max} was used. The extrapolated increase in rosiglitazone, warfarin and omeprazole exposure (AUC) was estimated to be 1 ie indicating no interaction.

Dabrafenib was also shown to induce human CYP3A4 and CYP2B6 in hepatocytes (Study CD2008/01428/00).

Dabrafenib was shown to be an *in vitro* substrate for human P-glycoprotein (Pgp) and murine breast cancer resistance protein 1 (BCRP1) efflux transporters *in vitro* (studies UH2008/00115/02 and UD2010/00042/00). The oral clinical bioavailability of dabrafenib was 95% (Study BRF113479), indicating that these efflux transporters have minimal impact on bioavailability. Dabrafenib and its metabolites were not inhibitors of Pgp *in vitro* (studies 2009/00143/01 and 2011N119324-01). Dabrafenib and M8 and M7 were shown to be inhibitors of BCRP, while M4 did not inhibit BCRP (Studies 2011N112849-00 and 2011N119323-00).

Dabrafenib inhibited human OATP1B1 and OATP1B3 in vitro with calculated IC_{50} values of 1.4 µM and 4.7 µM, respectively (Study CD2009/00116). Metabolite M7 (0.1 to 100 µM) inhibited human OATP1B1 and OATP1B3 in vitro with calculated IC_{50} values of 4.3 µM and 23 µM, respectively. Metabolite M4 (0.1 to 100 µM) inhibited human OATP1B1 and OATP1B3 in vitro with calculated IC_{50} values of 18 µM and 20 µM, respectively. Metabolie M8 (0.1 to 100 µM) inhibited human OATP1B1 and OATP1B3 *in vitro* with calculated IC_{50} values of 0.83 µM and 4.3 µM, respectively (Studies 2010N110986, 2010N110987 and 2010/00386/00).

Dabrafenib, M7 and M8 inhibited OAT1 with IC_{50} values of 6.9 μM, 29 μM and 10 μM, respectively. Dabrafenib and its three metabolites inhibited OAT3 with IC_{50} values of 3.4 μM, 7.3 μM, 9.0 μM and 3.4 μM, respectively (Study 2012N131808 01).

An *in vivo* study (BRF112680) with oral midazolam has been performed with repeated doses of dabrafenib. The study was performed with the gelatine capsule and not the final formulation, HPMC capsules. The gelatine capsule gives lower exposure (30%) than the HPMC capsule. The results showed a decrease in the exposure of a single dose of midazolam by 61% and 74% for C_{max} and AUC, respectively.

Study BRF113771 is an ongoing 4-part *in vivo* study (in 4 separate cohorts of subjects) designed to evaluate the effects of repeat dose dabrafenib on the single dose pharmacokinetics of warfarin, the effects of repeat dose oral ketoconazole and oral gemfibrozil on the repeat dose pharmacokinetics of dabrafenib and the repeat dose pharmacokinetics of dabrafenib in subjects with BRAF mutant solid tumors. Part A evaluates the effect of dabrafenib on S-warfarin, a CYP2C9 substrate. Parts B and C evaluate the effect of ketoconazole, a potent CYP3A4 inhibitor, and gemfibrozil, a CYP2C8 inhibitor, on dabrafenib. Partial PK results are available from Part B. Seven out of 12 patients has completed part B. Administration of ketoconazole resulted in an increase in both C_{max} and AUC for dabrafenib, with 26% and 57% respectively. For the metabolites the increase on Cmax and AUC was as follows: 17% and 48% for M7, 54% and 61% for M8 for Cmax and AUC respectively and 33% for M4 for both C_{max} and AUC.

Pharmacokinetics using human biomaterials

N/A

2.4.3. Pharmacodynamics

Mechanism of action

Primary and Secondary pharmacology

Tumour biopsies were collected in Study BRF112680 for immunohistochemistry staining analysis at baseline and 1 to 2 weeks of dosing in 8 evaluable subjects who received doses of 70 to 200 mg BID of dabrafenib. The median (range) decrease in pERK expression from baseline was 83.9% (38.0%, 93.3%) in subjects with BRAF V600 mutation-positive metastatic melanoma, indicating inhibition of the enzymatic pathway. Six out of 8 subjects showed ≥80% inhibition of the pERK pathway. The relationship between systemic effective concentration and % pERK inhibition was characterized using a maximum response (E_{max}) model with 100% maximum inhibition and an IC50 of 134 ng/mL (95% CI: 92.7, 155). The percent change in pERK was predicted by total daily dose on the basis of the mean pre-dose concentrations (C_T) observed on Day 15. A dose-related decrease in pERK was predicted with total daily doses <200 mg (100 mg BID) dabrafenib, with a plateau occurring beyond total daily doses of 200 mg. Administration of 150 mg BID was predicted to provide, on average, near maximum predicted inhibition of this target (approximately 80%) based on the E_{max} model.

FDG-PET imaging was performed at Screening and at Week 2 in a subset of subjects enrolled in the dose escalation part of FTIH study (BRF112680) following doses of 35 mg once daily up to 300 mg BID. A decrease in mean maximum standardized uptake value (SUVmax) was observed in 53 out of 56 subjects, with a median 60% decrease inSUVmax (percent change from baseline range -100% to +19%) across all doses. The decrease from baseline in sum of SUVmax (sum of the maximum uptake measured intarget lesions) was generally dose-related, except at 35 mg BID and 200 mg BID. The mean percent change from baseline ranged from -19 to -58% across the different cohorts. Decreases in FDG-PET uptake were related to the daily dose administered using aninhibitory Emax model. The median (95% bootstrap CI) total daily dose resulting in 50% of maximum response (ED50) was 214 mg (168, 312). There was no apparent benefit of a TID vs. a BID regimen.

In terms of secondary pharmacology, an exposure-response analysis was conducted to determine the relationship between the independently manually-read QTc interval and time-matched plasma concentrations of dabrafenib using a nonlinear mixed effects model. Data were available from 108 subjects (869 observations) receiving total daily doses of 12 mg to 600 mg dabrafenib in part 1 of study BRF112680 (gelatin capsules). Ten persons received 300 mg BID of gelatin capsules, the dose corresponding to the applied dosage of 150 mg BID of HPMC capsules. The predicted median changes in QTcP (QT duration corrected using an estimated population factor) at the maximum C_{max} value with the recommended part 2 dose and at the highest dose administered (300 mg BID) were ≤0.5 msec. Of note, one of two subjects in the all treated population in this study that had QTcF (QT duration corrected for heart rate by Fridericia's formula) interval increases to ≥501 msec, was the same subject that erroneously received daily doses of 900 mg (300 mg TID, gelatin capsules) instead of 300 mg (100 mg TID) of dabrafenib throughout the PK sampling period.

The analysis was also conducted by examining the relationship between QTcP and each of the metabolites. The slope of the exposure-response relationship for QTcP and dabrafenib metabolites was positive for all three metabolites. Based on the geometric mean C_{max} value observed at the recommended dose of 150 mg BID and at the highest dose administered in this study, 300 mg BID, the median change in QTcP was predicted to be ≤5.5 msec.

2.4.4. Discussion on clinical pharmacology

Based on exposure, relative potency, and pharmacokinetic properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib; while the activity of carboxy-dabrafenib is not likely to be significant. In most pharmacokinetic studies, the three major metabolites were quantified as well as parent dabrafenib. The metabolism of dabrafenib and its metabolites, and the metabolite pharmacokinetics in plasma are considered sufficiently well characterised by *in vitro* studies, mass-balance data and other clinical pharmacology studies.

Dabrafenib has low solubility and high permeability (BCS class II). As dabrafenib solubility is pH-dependent, its bioavailability might possibly be affected by concomitant administration of medicines such as proton pump inhibitors that increase gastric pH. Based on these theoretical considerations, the SmPC contains a warning that concomitant administration of dabrafenib with such medicines should be avoided. In addition, the CHMP requested the applicant to perform an in vivo study to investigate the interaction between pH-altering agents (e.g., proton pump inhibitor) and dabrafenib (the same cohort of subjects will be used to evaluate the effect of repeat dose of rifampin, a strong CYP3A4 inducer on dabrafenib).This issue is covered in the RMP.

The effect of food on dabrafenib was modest. With a high-fat meal, there was a 30% decrease in single-dose AUC. This food effect was detected as compared with a very long fast (10+4 hours) compared with the 2+1 hours fast recommended in clinical practice. A preliminary evaluation indicated that in clinical practice, the effect of a moderate-fat meal at steady state is negligible. However, the latter analysis was performed with the early gelatin capsule and the effect of a moderate-fat meal on the HPMC capsule is unknown. The SmPC recommends that dabrafenib should be administered at least 1 hour before or 2 hours after food, since this was the recommendation used in Phase III.

The effect of bodyweight on total active moiety has not been predicted. However, given the overall variability, it is agreed that the effect of bodyweight is not clinically relevant.

Dose adjustments in the elderly do therefore not seem to be necessary from a pharmacokinetic point of view.

There are insufficient data to evaluate the potential effect of race on dabrafenib pharmacokinetics.

Studies in patients with hepatic or renal impairment are ongoing. The applicant is recommended to determine free fraction at a few time points in all patients in the normal function and severe dysfunction groups, respectively. If a significant effect on free fraction of dabrafenib is seen in patients with severe organ dysfunction, evaluation of free fraction in the moderate impairment and possibly mild impairment groups will be necessary, and therefore sampling should be planned accordingly. Awaiting the final study reports, the SmPC contains adequate warnings to reflect that dabrafenib should be used with caution in patients with severe renal impairment and in patients with moderate or severe hepatic impairment. The pharmacokinetic study in patients with renal or hepatic impairment is included in the RMP.

Dabrafenib and its active metabolites appear to be primarily eliminated via metabolism (mainly CYP2C8 and 3A4 for dabrafenib, CYP3A4 for metabolites) but also to some extent via biliary excretion. Elimination of active moiety via the kidneys is negligible.

Interim data from the study BRF113771 with the CYP3A4/Pgp inhibitor ketoconazole indicate a relatively modest effect on dabrafenib, M7 and M8 (about 60% increase in AUC). The applicant was recommended to submit the final results of the study which are expected to be available in 2Q2013. In addition, the SmPC contains relevant warnings for inhibitors and inducers of CYP2C8 and 3A4. Dabrafenib has been shown to induce its own metabolism and a study with midazolam showed that it is a strong inducer of CYP3A4. *In vitro* data indicated that dabrafenib may be an inducer via PXR as well as CAR, and, thus, transport proteins in addition to several phase I (CYPs) and phase II (e.g. UGTs) metabolising enzymes may be affected. This might have large implications on the use of concomitant drugs, which has been sufficiently addressed in the SmPC.

Although the net effect of dabrafenib on CYP3A4 substrates appears to be induction at steady state, there is a risk of inhibition of CYP3A4 during the first days of treatment with dabrafenib, before full induction is obtained, as dabrafenib also appears to be a metabolism-dependent inhibitor of CYP3A4. The CHMP requested the applicant to perform a study in order to evaluate the effect of repeat dose of rifampin, a strong CYP3A4 inducer on the repeat dose of dabrafenib. This study is included in the RMP.

Furthermore, inhibition of OATP1B1/OATP1B3 by dabrafenib cannot be excluded and the applicant should perform an interaction study with an OATP1B1/OATP1B3 substrate, such as rosuvastatin. Until these data are available, the SmPC include relevant warnings. In addition, as dabrafenib is metabolised more than 25% the applicant will perform *in vitro* studies in order to further investigate if dabrafenib and its active metabolites are substrates for OATP1B1 and OATP1B3. These issues are covered in the RMP.

The results of exposure/response analysis indicate that at the 150 mg BID dose, the majority of subjects are likely at the top of the exposure-response relationship (i.e. near Emax). No strong relationships between AEs and exposure, except for pyrexia, were evident. Due to auto-induction, increase in exposure was less than dose-linear, and in the dose escalation study, an MTD was not reached.

2.4.5. Conclusions on clinical pharmacology

In general, the Applicant has sufficiently described the pharmacokinetics of dabrafenib. The pharmacodynamic effects of dabrafenib are well demonstrated in studies in both healthy subjects and the proposed target population.

2.5. Clinical efficacy

Three studies were submitted in support of the use of dabrafenib in the claimed indication, i.e. treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation:

Table 11 Development Program for Dabrafenib as Monotherapy in Metastatic Melanoma as of the Clinical Cut-off Dates for Each Study

Study Identifier	Protocol Name	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	BRAF Mutation Status at Enrollment [b]	Total No. of Subjects by Group Entered/ Completed
BREAK-3 (BRF113683)	A Phase III randomized, open-label study comparing dabrafenib to DTIC in previously untreated subjects with BRAF mutation positive metastatic melanoma	Dabrafenib (HPMC) 150 mg BID (dose may be reduced); oral; DTIC 1000 mg/m² every 3 weeks; continued treatment until disease progression, death or unacceptable adverse event	V600E: 249 V600K: 1[a]	Dabrafenib 187 enrolled 80 completed DTIC 63 enrolled 46 completed
BREAK-MB (BRF113929)	A Phase II open-label, two-cohort, multicenter study of dabrafenib as a single agent in treatment naïve and previously treated subjects with BRAF mutation-positive metastatic melanoma to the brain	Dabrafenib (HPMC) 150 mg BID (dose may be reduced); oral; continued treatment until disease progression, death or unacceptable adverse event	V600E: 139 (Cohort A: 74; Cohort B: 65) V600K: 33 (Cohort A: 15; Cohort B: 18)	172 Enrolled Cohort A: 89 enrolled 63 completed Cohort B: 83 enrolled 56 completed
BREAK-2 (BRF113710)	A Phase II single-arm, open-label study of dabrafenib in BRAF mutant metastatic melanoma	Dabrafenib (Gelatin) 150 mg BID (dose may be reduced); oral; continued treatment until disease progression, death or unacceptable adverse event	V600E: 76 V600K: 16	92 enrolled/ 59 completed

a. Randomized in error and did not receive treatment; included in ITT population but not the Safety Population.
b. An allele-specific real-time PCR assay was utilized to specifically detect the BRAF V600E vs. V600K mutation.

Dose response study

Study BRF112680

The selected dose of dabrafenib (150 mg BID) for further phase II and III clinical studies was chosen based on results from Study BRF112680, which was a Phase I, open-label, multiple-dose, dose-escalation study that investigated the safety, pharmacokinetics, and pharmacodynamics of dabrafenib in subjects with BRAF V600 mutation positive melanoma or other solid tumors.

BRF112680 was a 2-part study in which Part 1 identified the recommended Part 2 dose using a dose-escalation procedure. Dose escalation was designed to proceed until target clinical activity or PD activity was observed, until the maximum tolerated dose (MTD) was reached, or until further dose escalation was predicted to not provide sufficient increase in exposure. The recommended

dose and regimen for Part 2 was selected based on the safety, PK, and pharmacodynamic (PD) profiles observed after the treatment of subjects with BRAF V600 mutation positive melanoma. Daily doses of 12 mg (12 mg once daily) to 600 mg (300 mg BID) in 10 cohorts in Part 1 were investigated (gelatin capsules). PD endpoints obtained in Part 1 included tumour biomarkers, fluorodeoxyglucose-positron emission tomography [FDG-PET], tumour size, and response rate. Part 2 explored further the safety, tolerability, and clinical activity of the recommended dose (150 mg BID) and a lower dose (50 mg BID) of dabrafenib in subjects with V600 BRAF mutation-positive tumours (gelatin capsules).

The response rate (CR + PR) at Week 9 reported by the investigators for subjects in the Dose-Escalation Tumor Response Population in Part 1 of Study BRF112680 is presented in Table 12.

Table 12 Investigator-assessed Response at Week 9 for the Dose-Escalation Tumor Response Population in Part 1.

Summary of Investigator-Assessed Response at Week 9 for the Dose-Escalation Tumor Response Population in Part 1 (Unconfirmed Best Response)									
			Number of Subjects (%)					Response Rate	
Cohort	Dose Regimen	n	CR	PR	SD	PD	Unknown	CR+PR, n (%)	95% CI
1 + 2	≤35 mg once daily	3	0	0	3 (100)	0	0	0	-
3	35 mg BID	5	1 (20)	2 (40)	2 (40)	0	0	3 (60)	14.7, 94.7
4	70 mg BID	14	0	3 (21)	9 (64)	2 (14)	0	3 (21)	4.7, 50.8
5	100 mg BID	9	0	4 (44)	4 (44)	1 (11)	0	4 (44)	13.7, 78.8
6	100 mg TID	14	1 (7)	3 (21)	6 (43)	4 (29)	0	4 (29)	8.4, 58.1
7	150 mg BID	16	0	8 (50)	6 (38)	2 (13)	0	8 (50)	24.7, 75.3
8	200 mg BID	16	1 (6)	5 (31)	5 (31)	4 (25)	1 (6)	6 (38)	15.2, 64.6
9	300 mg BID	10	0	9 (90)	0	1 (10)	0	9 (90)	55.5, 99.7
10[a]	75/150 mg BID	5	0	1 (20)	3 (60)	1 (20)	0	1 (20)	0.5, 71.6

a. Subjects in Cohort 10 received 75 mg BID GSK2118436 for at least 15 days for PK assessments and were permitted to dose-escalate to 150 mg BID GSK2118436 thereafter.

PD = progressive disease

The response rate was 55% (95% CI: 31.5, 76.9) in subjects with metastatic melanoma without untreated brain metastases and 40% (95% CI: 12.2, 73.8) in those with asymptomatic, untreated, brain metastases treated at 150 mg BID. The median PFS was 6.31 months (95% CI: 3.48, 10.81) in subjects without untreated brain metastases and 4.21 months (95% CI: 3.32, 5.26) in those with untreated brain metastases.

Nine of 10 subjects with asymptomatic, untreated, brain metastases had a decrease in brain lesion size, and 4 of 10 subjects achieved complete resolution of all brain lesions. A decrease in the size of extracranial metastases was observed in all 9 subjects with responding brain lesions.

The response rate was 59% (95% CI: 32.9, 81.6) for subjects with V600E-mutation positive melanoma without untreated brain metastases treated with 150 mg BID dabrafenib and 17% (95% CI: 3.6, 41.4) for those treated with 50 mg BID.

A total of 24 subjects (21%) experienced SAEs during the first 9 weeks of treatment in Part 1. The most common SAE was cutaneous SCC, which occurred in 9 subjects (8%). The incidence of SAEs in the first 9 weeks was highest at the 300 mg BID dose cohort (50%). The MTD was not reached in this study. In terms of safety, there were no discontinuations of study treatment or deaths due to AEs (fatal SAEs) in the study.

2.5.1. Main study

BREAK-3 (BRF113683)

This was a Phase III randomized, open-label study comparing dabrafenib to DTIC in previously untreated subjects with BRAF mutation positive advanced (Stage III) or metastatic (Stage IV) melanoma. The BREAK-3 study was conducted in 12 countries in the US, European Union, Canada, Russian Federation and Australia.

Methods

Study Participants

Main inclusion criteria:

• Histologically confirmed unresectable Stage III or metastatic (Stage IV) BRAF V600E mutation positive melanoma

• Treatment naïve for advanced (unresectable Stage III)/metastatic disease (with exception of IL-2, surgery, and radiotherapy which were allowed)

• Measurable disease per Response Evaluation Criteria In Solid Tumours (RECIST) in solid tumours

• Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1

• Protocol specified criteria for adequate organ function.

Main exclusion criteria:

• 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. Subjects who had been disease-free for 5 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma were eligible

• 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, including: QTc ⩾480 msec; history of acute coronary syndrome (including unstable angina), coronary angioplasty, stenting, or cardiac arrhythmias (except sinus arrhythmia) within past 24 weeks; New York Heart Association Class II-IV heart failure; or abnormal valve morphology documented by echocardiogram.

Treatments

Eligible subjects were randomized to receive oral dabrafenib 150 mg BID or intravenous DTIC 1000 mg/m^2 every 3 weeks (Figure x). Subjects were evaluated for disease progression at Week 6, Week 12, Week 21, Week 30, Week 39, Week 48 and every 12 weeks thereafter. Subjects continued on treatment until radiologic disease progression, death, the occurrence of an unacceptable adverse event (AE), or withdrawal from the study.

Due to the open-label nature of the study, an independent radiology review, blinded to treatment assignment, was performed during the conduct of the trial. Subjects randomized to DTIC treatment were allowed to receive dabrafenib after initial radiologic progression was confirmed by independent review. Subjects were then followed for response, progression, survival, and further anti-cancer therapy while receiving dabrafenib, and for survival and further anti-cancer therapy after progression while on dabrafenib.

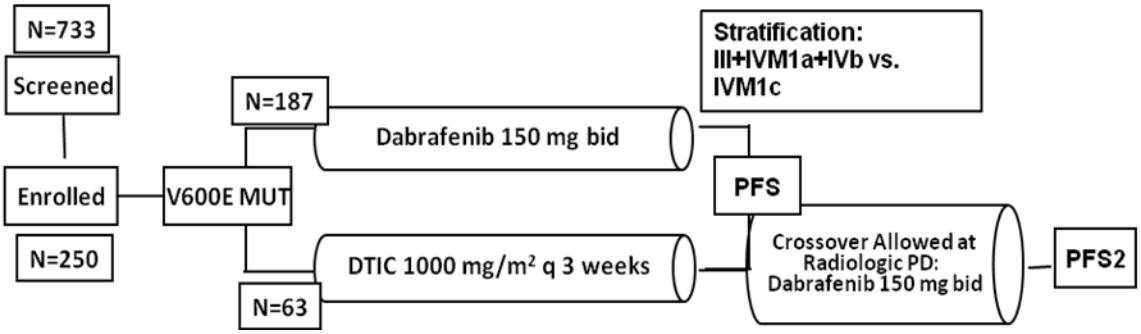


Figure 02 Study Design for Study BREAK-3

Objectives

The primary objective of the study was to establish the superiority of dabrafenib over DTIC with respect to Progression Free Survival (PFS) in subjects with advanced or metastatic BRAF V600E mutation positive melanoma.

Secondary objectives included comparison of Overall Survival (OS) and Overall Response Rate (ORR) between treatment groups, assessment of duration of response, assessment of the best ORR and PFS of subjects in the DTIC treatment group after initial progression and subsequent crossover to dabrafenib, evaluation of the safety and tolerability of dabrafenib and evaluation of HRQOL status.

Outcomes/endpoints

The primary efficacy endpoint was PFS, defined as the time from randomization until the first date of either objective disease progression or death due to any cause. Disease progression was based on radiographic or photographic evidence, and assessments made by the investigator according to RECIST v1.1.

The key secondary endpoints were the following:

-OS, defined as the time from randomization to death due to any cause.

-PFS2, defined for subjects randomized to the DTIC treatment group as the time to progression or death after cross-over to dabrafenib after initial progression on DTIC.

-Overall Response Rate (ORR), defined as the percentage of subjects achieving either a Complete or Partial tumour Response (CR/PR).

-ORR in subjects who cross over to dabrafenib after initial progression on DTIC.

-Duration of response, for those subjects who show a complete or partial tumour response, defined as the time from first documented evidence of CR or PR until the first documented sign of disease progression or death due to any cause.

-Duration of response in subjects who cross-over to dabrafenib after initial progression on DTIC.

-Validation of BRAF mutation assay for regulatory approval and registration.

Sample size

The sample size was based on the hypothesized differences in PFS between the two treatment arms.

In particular, the study had statistical power to detect a 67% reduction in risk of progression or death (corresponding to a hazard ratio of 0.33) in subjects who received dabrafenib (median PFS of 6 months) compared with subjects who receive DTIC (median PFS of 2 months. To show a 200% improvement in median PFS, the required number of PFS events to achieve statistical power of 99.7% was 102. To achieve 102 events, it was estimated that the study should include 200 subjects. At clinical cut-off 250 subjects had been enrolled in the study. 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.

Randomisation

Eligible subjects were randomized 3:1 to receive oral dabrafenib 150 mg BID or intravenous DTIC 1000 mg/m^2 every 3 weeks. Randomization was stratified according to disease staging at study entry (unresectable III+IVM1a+IVb vs. IVM1c).

Blinding (masking)

This was an open-label study.

Statistical methods

The primary endpoint was analysed using the stratified log-rank test, stratified for the randomisation factors. The following censoring rules applied:

• If two or more scheduled assessments were missing or not evaluable followed by an assessment of PD, PFS was censored at the last adequate assessment prior to PD or death.

• If anti-cancer therapy was started without evidence of documented disease progression or was started prior to documented progression, then PFS was censored at the date of the last radiological assessment that was no later than the date of initiation of anti-cancer therapy. If an assessment occurred on the same day as the start of new anti-cancer therapy, that assessment was used for censoring assuming that the assessment occurred prior to the administration of new anti-cancer therapy. The date of response at that assessment was used for censoring.

• If a subject had only a baseline visit or did not have a date of radiological scan that was no later than the date of initiation of anti-cancer therapy, PFS was censored at the date of randomization. If a subject had not progressed or died, then PFS was censored at the date of the last adequate assessment, defined as an assessment at which the investigator-determined response was CR, PR, or SD. The date of response was used as the censoring date.

No interim analysis of PFS was performed.

Sensitivity analysis

• Analysis including symptomatic progressions: In this analysis symptomatic progression was defined as a PFS event (rather than censoring at the time of symptomatic progression).

• Ignoring extended loss to follow-up and start of new anticancer therapy.: In this analysis subjects who have neither progressed nor died were censored from the PFS analysis at the date of the last radiological scan assessed by the investigator, regardless of whether missing assessments or initiation of new anti-cancer therapy prior to documented progression.

• Stepwise Cox Proportional Hazards Model Regression with Prognostic Factors as Covariates: Subjects are randomized and stratified for disease stage at screening (unresectable III+IVM1a+IVM1b vs. IVM1c). However, there are additional baseline and disease history factors that are well documented and are historically correlated with survival and, as such, are prognostic for the management of melanoma patients. The Cox proportional hazards model used a stepwise procedure in which the treatment remained in the model, disease stage was included as the stratification variable, and selected prognostic factors (age, sex, presence of visceral disease, baseline LDH, ECOG performance status, number of disease sites) were investigated using entry and removal significance levels of 0.05.

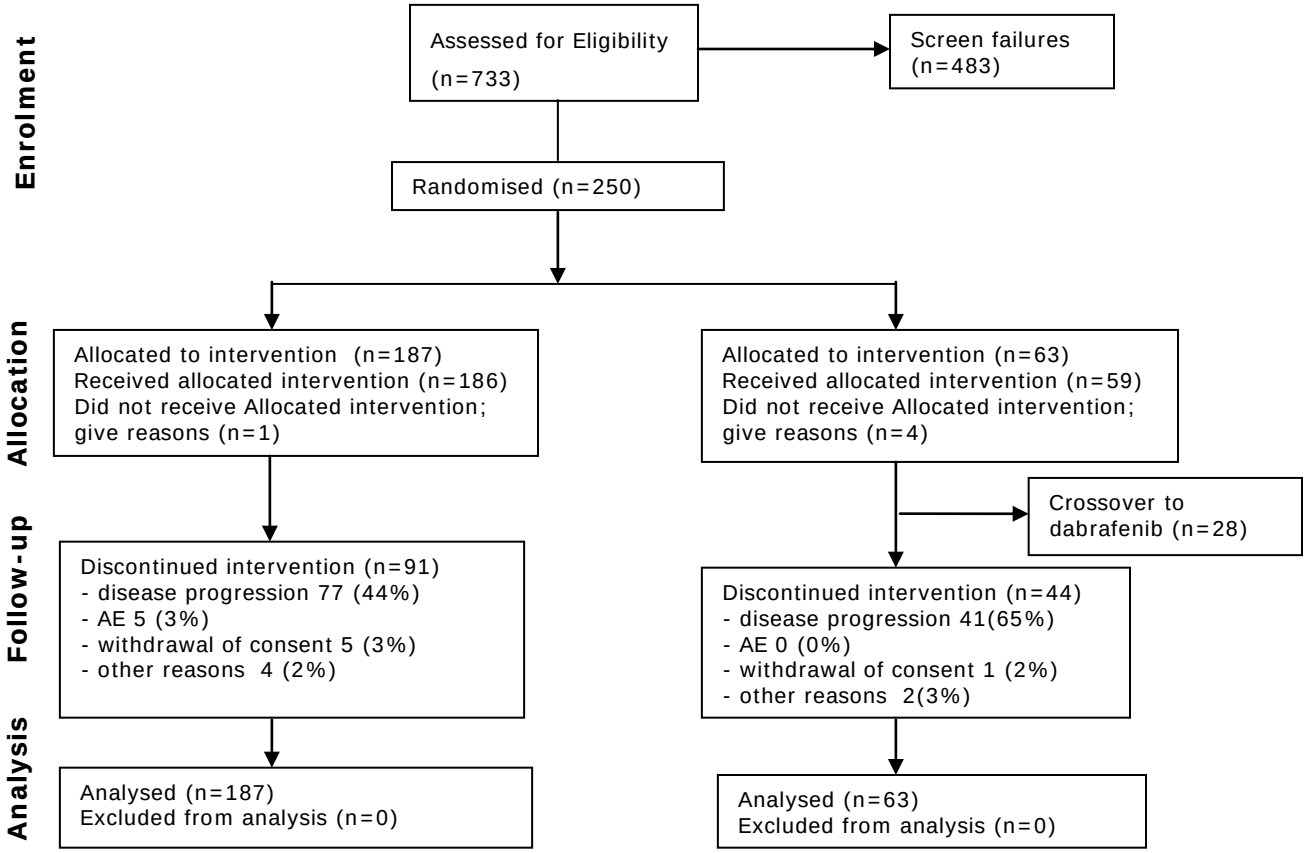
• Post-hoc analysis - visit-based sensitivity analysis (potential effect of off-schedule assessments): In this analysis progression dates were set to the protocol-defined visit timepoints for on-schedule assessments (defined as ±7 days for the protocol-defined assessment schedule) or were set to the next visit timepoint if the assessment occurred off-schedule (outside of the visit window). The same rules were applied for censoring dates, except that the actual date of the assessment was used if the assessment occurred off-schedule. In the event of death, the actual date was used in the analysis.

Subgroup analysis

PFS by subgroup was analysed according to number of metastatic disease sites (<3 or ≥3]), ECOG PS (=0 or ≥1), visceral disease (yes or no); baseline lactate dehydrogenase (LDH) [≤ upper limit of normal (ULN) or >ULN]; age (<65 or ≥65); sex and disease stage (IVM1c or III, IVM1a and IVM1b).

Results

Participant flow



Recruitment

The first patient was enrolled on 2 February 2011 and the last one was enrolled on 1 September 2011.

Conduct of the study

There were 6 protocol amendments after study initiation described in Table 13:

Table 13 Summary of Protocol Amendments

Date	Summary of amendement
3 Nov 2010	Amendment No.1: Modification to contraception section based upon nonclinical tox; Addition of CT for respiratory symptoms to dose modification table; Change to slide

	requirements for tumor tissue testing (20 to 15); Corrections to Table 10 and Table 11 time and events (typos and misalignment of response assessments); Statistical changes (mostlytypographical) addition of secondary malignancies as secondary objective; addition of QOL to crossover arm; cfDNA sample at progression changed from optional to mandatory.
4 Mar 2010	Amendment No. 02: A Country Level Amendment for France to modify the Tc stopping criteria in response to a request from the French regulatory agency, AFSSAPS.
23 Mar 2011	Amendment No.03 :Inclusion of serial PK sampling on a subset of patients to further characterize final formulation; clarification of crossover eligibility criteria; correction to time and events tables, specifically clarification of timing of assessments; modification to tumor tissue requirements to allow primary tissue for screening, clarification of QoL time points and allowing one questionnaire collection via phone; addition of statistical y objective to analyze at best overall response rate.
3 Jun 2011	Amendment No.04: Dose monitoring and management guidelines for neutropenia and fever have been updated based on recent reports of grade 4 neutorpenia and complicated pyrexia in patients on another BRAF study using HPMC capsules. Wording to allow collection of non-melanoma skin biopsy slides and pathology reports. Full body skin photos at baseline have been changed from required to recommended. Clarifications to Safety and Health outcomes endpoints. Wording to recommend PK collection for all SAEs. T&E Table 10 and Table 11: added a day 8 ANC and some corrections have been made. Dexamethasone added to cautionary medications.
14 Nov 2011	Amendment No. 05: Added treatment option that allows subjects with Investigator reported disease progression who are still benefitting from study treatment with GSK2118436 to continue study drug. Subjects must be willing to continue study procedures according to the Time and Events Table, and a consultation with the Medical Monitor is required. A guideline for renal insufficiency was added for the management of renal toxicities. Dose modification was updated to account for any Grade 3 toxicity recurrence. Added the collection of serum creatinine and BUN laboratory values for the management of fevers.
20 Apr 2012	Amendment No. 06 :The results of the planned primary analysis confirms that the primary endpoint of improved progression free survival in the GSK2118436 (dabrafenib arm) has been achieved. This data was reviewed with the IDMC and the committee has unanimously recommended that patients who were randomized to the DTIC arm of the study be allowed the option to receive dabrafenib prior to disease progression based on the judgment of the investigator. Independent review confirmation of disease progression will no longer be prior to crossover. IDMC added to the list of abbreviations. The crossover rules were updated. Time and Events table 13 was updated with requirement for re-establishing efficacy and safety baseline measures within 28 days of first dose of GSK2118436 and QOL requirement at crossover was clarified. Statistics section updated to reflect the current plans for analyses and address multiple testing issues. Wording was modified in the safety section to clarify intent in the collection of events of pyrexia and basal cell carcinoma.

Baseline data

Baseline demographics, baseline disease characteristics and prior anti-cancer therapy information are summarised in the tables 14, 15 and 16 respectively.

Table 14 Summary of Demographic Characteristics in the Randomized Population (ITT Population)

	Randomized Phase		Crossover
	GSK2118436 (N=187)	DTIC (N=63)	GSK2118436 (N=28)
Age (years)			
Mean	53.5	51.6	50.8
sd	13.76	14.22	14.39
Median	53.0	50.0	50.0
Min.	22	21	24
Max.	93	82	75
Sex, n (%)			
Female	75 (40)	26 (41)	12 (43)
Male	112 (60)	37 (59)	16 (57)
Ethnicity, n (%)			
Hispanic or Latino	7 (4)	0	0
Not Hispanic or Latino	180 (96)	63 (100)	28 (100)
Race			
White	186 (100)	63 (100)	28 (100)

Table 15 Summary of Disease Characteristics (ITT Population)

	Number (%) of Subjects	
	GSK2118436 (N=187)	DTIC (N=63)
Primary tumor type at Initial Diagnosis		
Melanoma	187 (100)	63 (100)
Tumor classification at Initial Diagnosis		
Cutaneous	165 (88)	56 (89)
Non-cutaneous	6 (3)	2 (3)
Other	3 (2)	0
Unknown	13 (7)	5 (8)
Stage at Screening		
IIIa	0	1 (2)
IIIb	1 (<1)	1 (2)
IIIc	6 (3)	2 (3)
IV	180 (96)	59 (94)
TNM staging at Screening: Distant metastasis		
M0	6 (3)	1 (2)
M1a	23 (12)	10 (16)
M1b	34 (18)	12 (19)
M1c	124 (66)	40 (63)
Visceral or non-visceral disease at Screening		
Visceral	22 (12)	8 (13)
Non-visceral	50 (27)	20 (32)
Visceral and non-visceral	115 (61)	35 (56)
ECOG PS at Baseline		
ECOG = 0	124 (66)	44 (70)
ECOG ≥1	62 (33)	16 (25)
Unknown	1 (<1)	3 (5)
Baseline LDH		
Equal to or below ULN	119 (64)	43 (68)
Above ULN	67 (36)	19 (30)
Unknown	1 (<1)	1 (2)

Table 16 Summary of Prior Anti-cancer Therapy (ITT Population)

	Number (%) of Subjects	
	GSK2118436 (N=187)	DTIC (N=63)
Any therapy	**181 (97)**	**62 (98)**
Surgery	179 (96)	61 (97)
Immunotherapy	52 (28)	15 (24)
Radiotherapy	37 (20)	10 (16)
Biologic therapy (monoclonal antibodies, vaccines)	3 (2)	3 (5)
Chemotherapy (cytotoxics, non-cytotoxics)	1 (<1)	4 (6)
Hormonal therapy	0	1 (2)
Number of immunotherapy regimens		
0	135 (72)	48 (76)
1	39 (21)	11 (17)
≥2	13 (7)	4 (6)
Number of chemotherapy regimens		
0	186 (>99)	59 (94)
1	1 (<1)	3 (5)
≥2	0	1 (2)
Number of biologic therapy regimens		
0	184 (98)	60 (95)
1	2 (1)	3 (5)
≥2	1 (<1)	0
Number of hormonal therapy regimens		
0	187 (100)	62 (98)
1	0	1 (2)
≥2	0	0

Numbers analysed

For the purpose of analysis, the following populations were defined:

- The Intent-to-Treat (ITT) (n=250) - all randomized subjects regardless of whether or not treatment was administered. This population was based on the treatment to which the subject was randomized.
- The Safety Population (n=246) - all randomized 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 randomized.
- The Crossover Population (n=28) - subjects who were randomized to the DTIC arm, and who elected at the point of disease progression to receive dabrafenib. Only subjects who received at least one dose of dabrafenib were included in the Crossover Population.

One subject in the dabrafenib ITT Population and 3 subjects in the DTIC ITT Population were excluded from the Safety Population since they did not receive any study treatment. Additionally, 1 subject who was randomized to treatment with DTIC only received dabrafenib and is analyzed in the dabrafenib Safety Population.

Outcomes and estimation

Primary endpoint

The efficacy results in terms of the primary endpoint of Progression Free Survival (investigator assessed) and for the primary analysis of 19 December 2011 and the updated PFS analysis of 25 June 2012, are summarised in the following table 17 and figures 3 and 4.

Table 17 Summary of Investigator-assessed Kaplan-Meier Estimates of Progression-free Survival (ITT Population)

	Data as of December 19, 2011		Data as of June 25, 2012	
	Dabrafenib N=187	**DTIC N=63**	**Dabrafenib N=187**	**DTIC N=63**
Progression-free survival				
Median, months (95 % CI)	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)	6.9 (5.2,9.0)	2.7 (1.5,3.2)
HR (95 % CI)	0.30 (0.18, 0.51) P < 0.0001		0.37 (0.24, 0.58) P < 0.0001	
Overall response[a]				
% (95 % CI)	53 (45.5, 60.3)	19 (10.2, 30.9)	59 (51.4, 66.0)	24 (14, 36.2)
Duration of response				
Median, months (95 % CI)	N=99 5.6 (4.8, NR)	N=12 NR (5.0, NR)	N=110 8.0 (6.6, 11.5)	N=15 7.6 (5.0, 9.7)

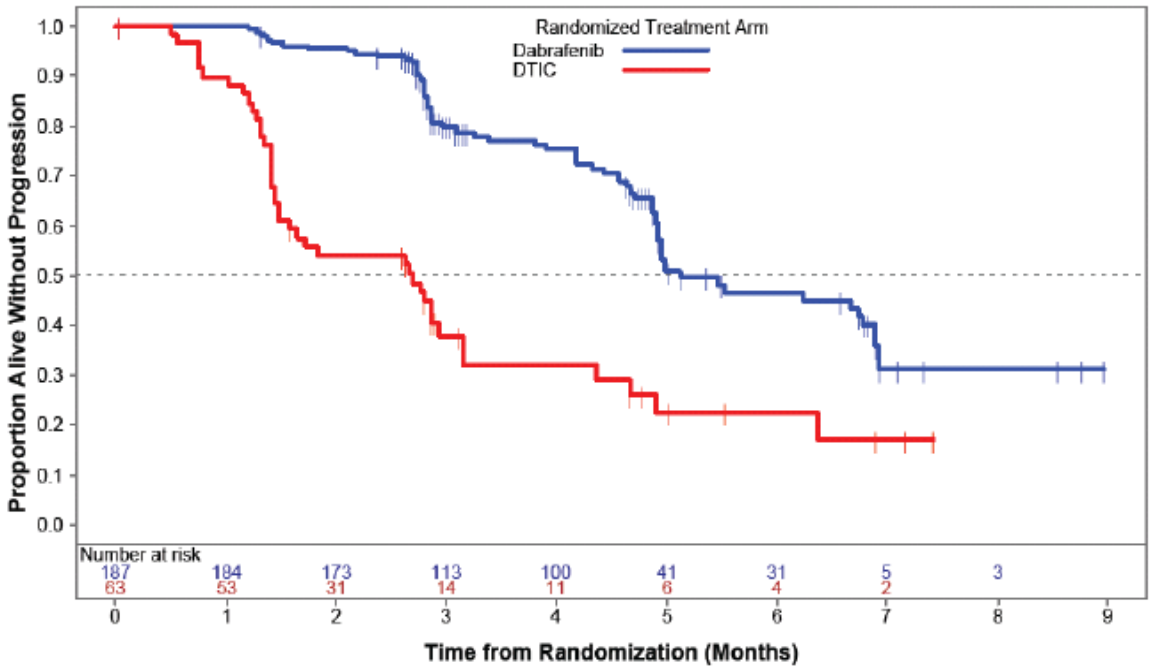


Figure 03 Investigator-assessed Kaplan-Meier Progression-free Survival Curves (ITT Population, cut-off date 19 December 2011)

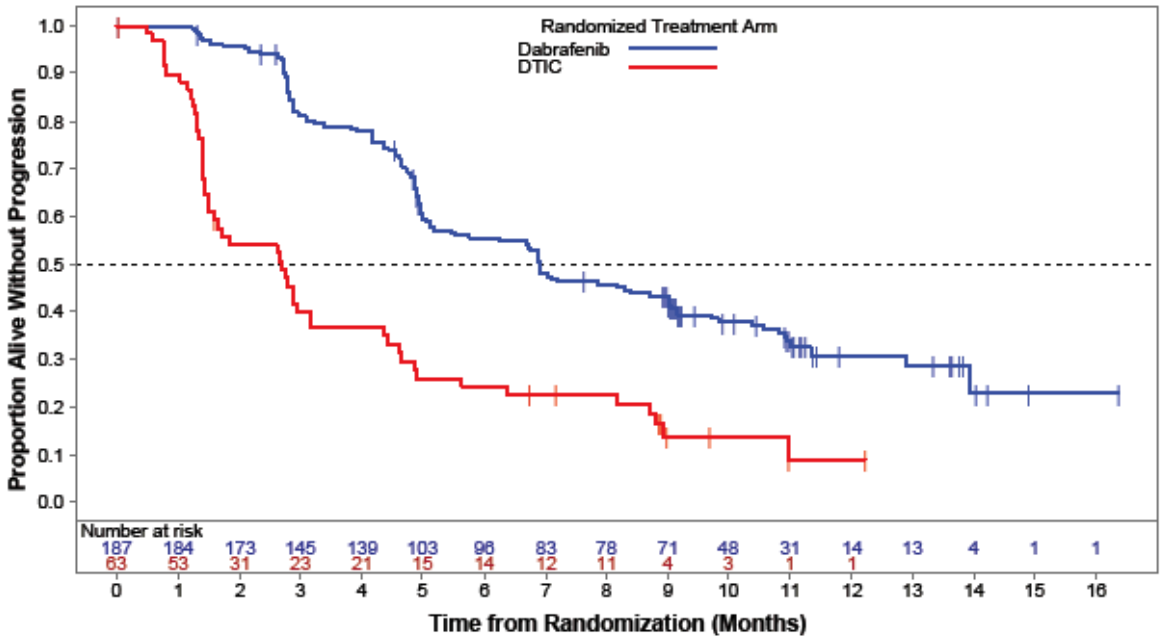


Figure 04 Progression-free Survival according to investigator, (ITT Population, cut-off date 25 June 2012)

Progression-free survival – independent radiologist-assessed

The PFS analysis was also performed by an independent radiologist (Table 18 and figure 5).

Table 18 Summary of Independent Radiologist-assessed Kaplan-Meier Estimates of Progression-free Survival (ITT Population)

	GSK2118436 (N=187)	DTIC (N=63)
Number of subjects, n (%)		
N	187	63
Progressed or died (event)	68 (36)	32 (51)
Censored, follow-up ended	22 (12)	15 (24)
Censored, follow-up ongoing	97 (52)	16 (25)
Estimates for progression-free survival (months)[a]		
1st quartile	4.6	1.4
95% confidence interval	(3.1, 4.9)	(1.3, 1.8)
Median	6.7	2.9
95% confidence interval	(5.0, 6.9)	(1.7, 4.9)
3rd quartile	8.8	NR
95% confidence interval	(6.9, 8.8)	(4.7, NR)
Adjusted hazard ratio[b]		
Estimate (95% confidence interval)	0.35 (0.20, 0.61)	

a. Quartiles estimated using the Brookmeyer-Crowley method.b. Hazard ratios were estimated using a Pike estimator. A hazard ratio <1 indicates a lower risk with dabrafenib compared with DTIC. Hazard Ratio and p-value from stratified log-rank test were adjusted for disease stage at screening.

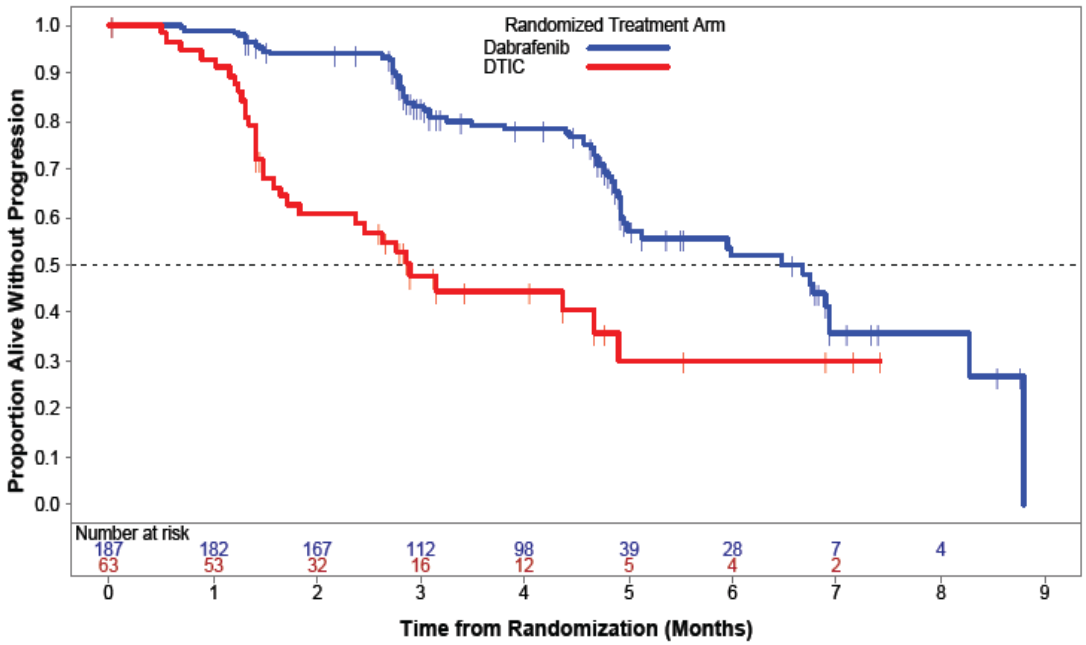


Figure 05 Independent Reviewer-Assessed Kaplan-Meier Progression-Free Survival curves

Key secondary endpoints

Results in terms of the key secondary endpoints of Overall Response, Overall Response Duration and Overall Survival, are summarised in the following tables and figures.

Table 19 Results of Overall Response and Overall Response Duration from the Pivotal Study BREAK-3

	Data as of December 19, 2011		Data as of June 25, 2012	
	Dabrafenib N=187	**DTIC N=63**	**Dabrafenib N=187**	**DTIC N=63**
Overall response[a]				
% (95 % CI)	53 (45.5, 60.3)	19 (10.2, 30.9)	59 (51.4, 66.0)	24 (14, 36.2)
Duration of response				
Median, months (95 % CI)	N=99 5.6 (4.8, NR)	N=12 NR (5.0, NR)	N=110 8.0 (6.6, 11.5)	N=15 7.6 (5.0, 9.7)

Table 20 Survival data from the primary and post-hoc analyses

Cut-off dates	Treatment	Number of deaths (%)	Median	Hazard Ratio (95% CI)	Number of cross- over patients (%)
December 19, 2011	DTIC	9 (14%)	NR [NR, NR]	0.61 (0.25, 1.48)[(a)]	28 (44%)
	dabrafenib	21 (11%)	NR [NR, NR]		
June 25, 2012	DTIC	21 (33%)	NR[NR, NR]	0.75 (0.44, .29) [(a)]	35 (56%)
	dabrafenib	55 (29%)	NR [11.3,NR]		
December 18, 2012	DTIC	28 (44%)	15.6 [12.7, NR]	0.76 (0.48, 1.21) [(a)]	36 (57%)
	dabrafenib	78 (42%)	18.2 [16.6, NR]		

[(a)]Patients were not censored at the time of cross-over

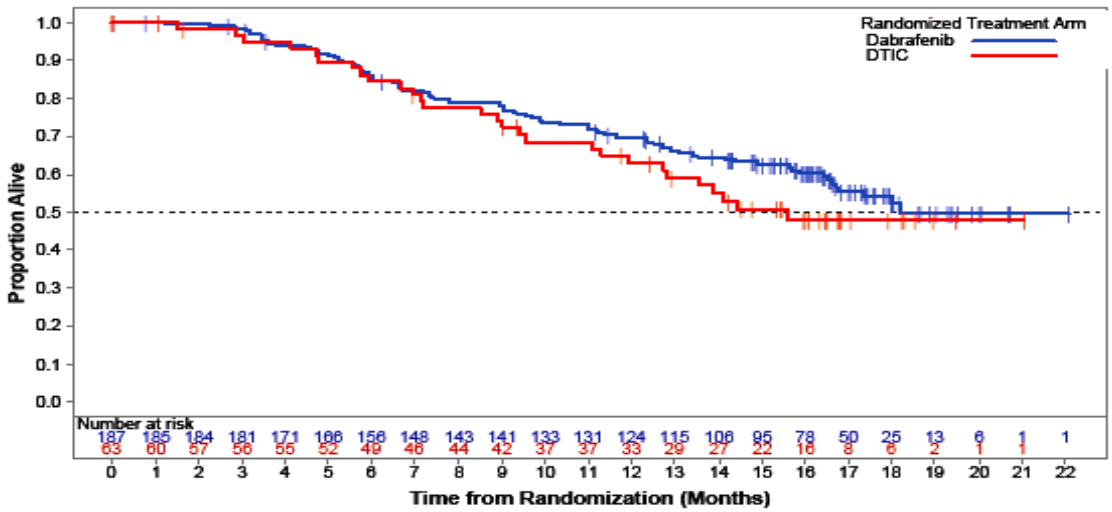


Figure 06 Kaplan-Meier Curves cut-off date 18 December 2012

Other secondary endpoints

Health-related quality of life

For the quality of life (QOL) assessment, both the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) and the EuroQol 5D (EQ-5D) questionnaires were administered to subjects at screening (before drug administration), Week 6, Week 12, Week 15, at disease progression, and at approximately 30 days (±7) after progression. At screening subjects in the two treatment arms showed comparable results of HRQOL as determined from both EORTCQLQ-C30 and EQ-5D (data not shown).

Regarding EORTCQLQ-C30, overall global health status scores showed similar profiles between the two treatment arms. For functionality scales and symptom scales the results were also comparable between the two treatment arms. However, scores related to “role functioning”, “social functioning” and “fatigue” were markedly better in the dabrafenib arm than in the DTIC arm. For EQ-5D, upon progression there was an increase in the percentage of subjects in both arms reporting “some problem” or “extreme problem” with all dimensions of the EQ-5D relative to screening For both questionnaires, the number of assessments decreased throughout the study. Consequently, meaningful data does not exist after Week 15.

Ancillary analyses

Results of the sensitivity analyses are presented in Figure 7.

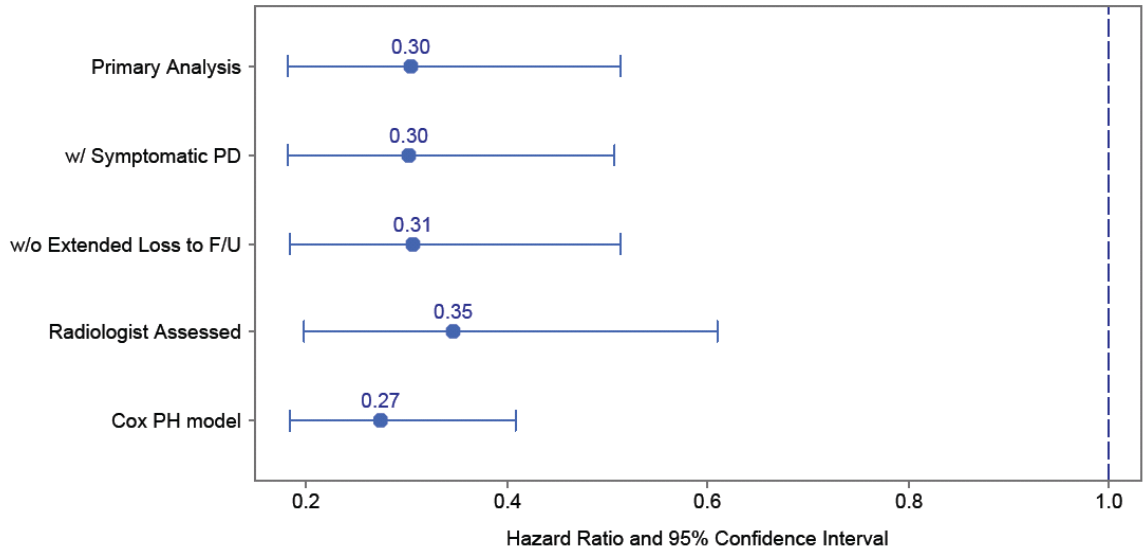


Figure 07 Hazard Ratios and 95% Confidence Intervals for Progression-Free Survival Including Sensitivity Analyses for Study BREAK-3 (ITT Population)

F/U: follow up; PD: progressive disease; PH: proportional hazard; Radiologist assessed: independent review; w: with, w/o – without.
Note: Hazard ratios were estimated using a Pike estimator adjusted for disease stage at screening. HR<1indicates a lower risk with dabrafenib compared with DTIC. Step-wise selection Cox model included baseline terms for: age, sex, LDH (above *vs.* below upper limit of normal), ECOG PS (0 *vs.* 1+), visceral disease (yes *vs.* no), and number of disease sites (<3 *vs.* ≥3).

The results of the subgroup analyses are summarized in Figure 8.

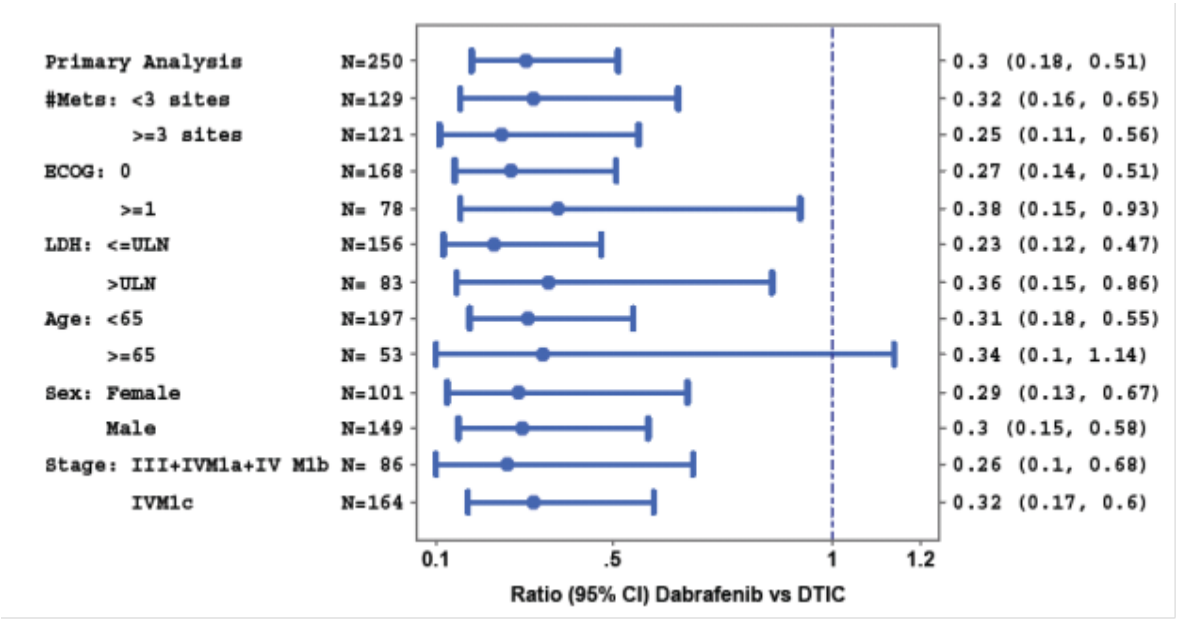


Figure 08 Hazard Ratios and 95% Confidence Intervals for Progression-free Survival Subgroup Analyses (ITT Population)

Note: Hazard ratios are estimated using a Pike estimator adjusted for disease stage at screening, except for disease stage subgroups. A hazard ratio <1 indicates a lower risk with dabrafenib compared with DTIC.

Summary of main study

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

Table 21 Summary of Efficacy for trial BREAK-3 (BRF113683)

Title: A Phase III randomized, open-label study comparing dabrafenib to DTIC in previously untreated subjects with BRAF V600E mutation positive advanced (Stage III) or metastatic (Stage IV) melanoma			
Study identifier	BRF113683		
Design	multicentre, randomised, open label, double-blind		
	Duration of main phase:		Until disease progression or unacceptable toxicity
Hypothesis	Superiority		
Treatments groups	Dabrafenib		150mg twice a day (N=187)
	DTIC		I.V. DTIC 1000mg/m^2 every 3 weeks (N=63)
Endpoints and definitions	Primary endpoint	Progression Free Survival (PFS)	Time between the date of randomization and the earlier of the date of disease progression or death due to any cause.
	Secondary	Overall Response Rate (ORR)	Percentage of subjects achieving either a confirmed CR or PR per RECIST by investigator assessment.

	Secondary	Duration of Response	Time from first documented evidence of PR or CR until the first documented sign of disease progression or death due to any cause.
	Secondary	Overall Survival (OS)	Time between the date of randomization and the date of death due to any cause.
Database lock	13/02/2012		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat population; 19/12/2011		
Descriptive statistics and estimate variability	Treatment group	Dabrafenib	DTIC
	Number of subjects	187	63
	Median PFS (months)	5.1	2.7
	95% CI	(4.9, 6.9)	(1.5, 3.2)
	ORR	53%	19%
	95% CI	(45.5, 60.3)	(10.2, 30.9)
	Duration of response (DOR)	5.6	NR
	95% CI	(4.8, NR)	(5.0, NR)
	Median OS (months)	NR	NR
	95% CI	(NR, NR)	(NR, NR)
Effect estimate per comparison	Primary endpoint: PFS	Comparison groups	Dabrafenib vs. DTIC
		Hazard ratio	0.30
		96% CI	(0.18, 0.53)
		P-value	<0.0001
	Secondary endpoint: ORR	Comparison groups	Dabrafenib vs. DTIC
		Difference in response rates	34%
		95% CI	(19.8%, 47.6%)
	Secondary endpoint: DOR	No comparison of the duration of response between treatment arms was done.	
	Secondary endpoint: OS	Comparison groups	Dabrafenib vs. DTIC
		Hazard ratio	0.61
		95% CI	(0.25, 1.48)
Notes	Stratification factors for the primary analysis (logrank test)		
Analysis description	**Updated Analysis**		

Analysis population and time point description	Intent to treat population; (25/06/2012 for PFS, ORR and DOR and 18 December 2012 for OS)		
Descriptive statistics and estimate variability	Treatment group	Dabrafenib	DTIC
	Number of subjects	187	63
	Median PFS (months)	6.9	2.7
	95% CI	(5.2, 9.0)	(1.5, 3.2)
	ORR	59%	24%
	95% CI	(51.4, 60.6)	(14, 36.2)
	Duration of response (DOR)	8.0	7.6
	95% CI	(6.6, 11.5)	(5.0, 9.7)
	Median OS (months)	18.2	15.6
	95% CI	(16.6, NR)	(12.7, NR)
Effect estimate per comparison	Primary endpoint: PFS	Comparison groups	Dabrafenib vs. DTIC
		Hazard ratio	0.37
		96% CI	(0.23, 0.58)
		P-value	<0.0001
	Secondary endpoint: ORR	Comparison groups	Dabrafenib vs. DTIC
		Difference in response rates	35%
		95% CI	(20.9%, 48.7%)
	Secondary endpoint: DOR	No comparison of the duration of response between treatment arms was done.	
	Secondary endpoint: OS	Comparison groups	Dabrafenib vs. DTIC
		Hazard ratio	0.76
		95% CI	(0.48, 1.21)

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

N/A

Clinical studies in special populations

N/A

Supportive studies

Two supportive phase II studies (BREAK 2 and BREAK-MB) were submitted.

Study BREAK-2

BREAK-2 was a single-arm, Phase II open-label study of metastatic melanoma in the BRAF V600E (primary) and BRAF V600K mutation positive populations. Key eligibility criteria included histologically confirmed metastatic melanoma (Stage IV) with BRAF (V600E and V600K) mutation, treatment-naïve or received prior systemic treatment in the metastatic setting and measurable disease according to RECIST (version 1.1), ECOG PS of 0 to 1.

Subjects received dabrafenib 150 mg BID and continued on treatment until disease progression, death, or unacceptable AE. After discontinuation of the study treatment, subjects remained on the study for follow-up assessments and updates to other anticancer treatments received until death. The primary objective for this study was to assess the ORR, defined as the proportion of subjects with investigator-assessed complete responses (CR) and partial responses (PR), after treatment with the oral dabrafenib in subjects with BRAF V600E mutation positive metastatic melanoma.

Results

A total of 92 subjects were enrolled in the study: 76subjects with V600E mutation positive metastatic melanoma and 16 subjects with V600K mutation positive metastatic melanoma.

The median age was 55.5 years, 53% of the subjects were male and the majority of subjects were white (99%). Most subjects (52%) had tumours in at least 3 organs, and the most common locations of disease were lymph nodes (61%), lung (47%), subcutaneous tissue (36%) and liver (34%). All subjects received some type of prior anti-cancer therapy including surgery, radiotherapy and other biologic, immune, hormonal or small molecule therapies.

As of the data cut-off date, 6 subjects (7%) had withdrawn from the study and 29 subjects (32%) died.

The key efficacy data is presented in Table 22.

Table 22 Key efficacy data from the supportive Study BREAK-2 (All Treated Subjects)

	All Treated Subjects Population	
Endpoints/ Investigator Assessment	**BRAF V600E (Primary) N=76**	**BRAF V600K N=16**
Overall response rate[a]		
% (95% CI)	59 (48.2, 70.3)	13 (0, 28.7)
Response duration		
Median, months (95% CI)	N=45 5.2 (3.9, NR)	N=2 5.3 (3.7, 6.8)
Progression-free survival		
Median, months (95% CI)	6.3 (4.6, 7.7)	4.5 (2.6, 6.2)
Overall survival		
Primary analysis at 6 months follow-up Median, months (95% CI)	9.5 (9.5, NR)	7.9 (5.5, NR)
Updated analyses at 12 months follow-up[b] Median, months (95% CI)	13.1 (10.4, NR)	12.9 (6.9, 17.1)

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

Study BREAK-MB

Study BREAK-MB was a global, multi-center, open-label, two-cohort, Phase II study designed to prospectively evaluate the activity of dabrafenib in subjects with histologically confirmed (Stage IV) BRAF-mutation positive (V600E or V600K) melanoma metastatic to the brain. Subjects were enrolled into Cohort A (subjects with no prior local therapy for brain metastasis) or Cohort B (subjects who had received prior local therapy for brain metastasis).

All subjects in the study received twice daily dosing of 150 mg dabrafenib (oral HPMC capsules) until evidence of disease progression, death, or unacceptable AEs.

The primary objective of the study was to assess the overall intracranial response rate (OIRR), defined as the proportion of subjects with confirmed complete or partial intracranial responses assessed by investigators in each of two cohorts of subjects with BRAF V600E mutation-positive metastatic melanoma to the brain treated with oral dabrafenib.

Results

A total of 172 subjects with V600 mutation-positive melanoma (V600E mutation: 139 subjects; V600K mutation: 33 subjects) were enrolled into the study (Cohort A: 89; Cohort B: 83) by 24 investigators in 6 countries.

The majority of subjects were <65 years old (82%), 70 % of the subjects were male, and all subjects were white. The majority of subjects (81%) across both cohorts had V600E mutation-positive melanoma, and slightly more than half (54%) had lactate dehydrogenase (LDH) >upper limit of normal (ULN) at baseline.

As of the clinical data cut-off date, 119 subjects had discontinued study treatment (Cohort A: 71%; Cohort B: 67%). The primary reason for discontinuation was disease progression (Cohort A: 69%; Cohort B: 55%). Overall, 14 (8%) subjects had withdrawn from the study. The most frequent reason for study withdrawal was withdrawal of consent.

The key efficacy data is presented in Table 23.

Table 23 Key Efficacy Data from Study BREAK-MB (All Treated Subjects)

	All Treated Subjects Population			
	BRAF V600E (Primary)		**BRAF V600K**	
	Cohort A N=74	**Cohort B N=65**	**Cohort A N=15**	**Cohort B N=18**
Overall intracranial response rate, % (95 % CI)[a]				
	39% (28.0, 51.2) P < 0.001[b]	31% (19.9, 43.4) P < 0.001[b]	7% (0.2, 31.9)	22% (6.4, 47.6)
Duration of intracranial response, median, months (95% CI)				
	N=29	N=20	N=1	N=4

	4.6 (2.8, NR)	6.5 (4.6, 6.5)	2.9 (NR, NR)	3.8 (NR, NR)
Overall response, % (95% CI)[a]				
	38% (26.8, 49.9)	31% (19.9, 43.4)	0 (0, 21.8)	28% (9.7, 53.5)
Duration of response, median, months (95% CI)				
	N=28 5.1 (3.7, NR)	N=20 4.6 (4.6, 6.5)	NA	N=5 3.1 (2.8, NR)
Progression-free survival, median, months (95% CI)				
	3.7 (3.6, 5.0)	3.8 (3.6, 5.5)	1.9 (0.7, 3.7)	3.6 (1.8, 5.2)
Overall survival, median, months (95% CI)				
Median, months	7.6 (5.9, NR)	7.2 (5.9, NR)	3.7 (1.6, 5.2)	5.0 (3.5, NR)

a. Confirmed response. b This study was designed to support or reject the null hypothesis of OIRR ≤10% (based on historical results) in favour of the alternative hypothesis of OIRR ≥ 30% in BRAF V600E mutation positive subjects.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The BREAK-3 pivotal study was appropriately designed with respect to patient population, comparator and study endpoints. There were no conventional dose-finding trials, but the rational for the selected dose is endorsed.

Efficacy data and additional analyses

Results from the pivotal study revealed a median PFS of 5.1 months for the dabrafenib group and 2.7 months for the DTIC group (HR: 0.30; 95% CI: 0.18, 0.53; p<0.0001). The benefit in PFS was much more pronounced in an updated analysis (cut-off of 25 June 2012), showing a median PFS of 6.9 months for the dabrafenib group versus 2.7 months for the DTIC group (HR=0.37; 95% CI: 0.24, 0.58; p<0.0001).

The analysis of ORR (CR+PR) further supported the PFS data as there was a difference in ORR of 35% in favour of dabrafenib compared to DTIC (95 % CI: 20.9, 48.7). In the updated OS analysis a trend in favour of dabrafenib is shown (HR=0.76, 95% CI: 0.48, 1.21).

Evaluation of Quality of life and patient reported outcome data did not give clear indications of improvement with dabrafenib over DTIC overall, although on certain items dabrafenib produced better results than DTIC. In an open label trial evaluation of QoL data may be confounded by investigators and patients bias. Consequently, the clinical relevance of the QoL assessment is considered limited.

The two phase II studies provided additional support concerning the anti-tumour effect of dabrafenib in subjects with BRAF V600 mutation: In BREAK-2, median PFS for subjects with BRAF V600E mutation was 6.3 months (95 % CI: 4.6, 7.7), and confirmed objective response was 59% (95 % CI: 48.2, 70.3). For subjects with BRAF V600K mutation median PFS was 4.5 months (95 % CI: 2.6, 6.2) and confirmed ORR was 13% (95 % CI: 0, 28.7). In BREAK-MB, the overall response rate in patients with BRAF V600E metastatic melanoma was 38 % (95 % CI: 26.8, 49.9) and 31% (95 5CI: 19.9, 43.4) for locally non-pretreated and pretreated patients, respectively. In patients with BRAF V600K mutation positive metastatic melanoma the response rate was 0 (95 % CI: 0, 21.8) and 28 % (95 % CI: 9.7, 53.5) for locally non-pretreated and pretreated patients, respectively.

Patients with melanoma driven by BRAF mutations other than V600E were excluded from the confirmatory trial however based on the results from the supportive studies dabrafenid inhibited also BRAF with mutation V600K as well although the activity appears lower than in V600E tumours. Therefore, the CHMP concluded that there was enough evidence to support a broader indication of "V600 mutation" and not to restrict the indication to BRAF V600E patient population.

It is important to note that there appears to be no benefit in patients which are BRAF WT. This is reflected in the SmPC under section 4.2: "The efficacy and safety of dabrafenib have not been established in patients with wild-type BRAF melanoma therefore dabrafenib should not be used in patients with BRAF wild-type melanoma'' and under section 5.1 of the SmPC where it is stated that ''Before taking dabrafenib, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test. In the Phase II and III clinical trials, screening for eligibility required central testing for BRAF V600 mutation using a BRAF mutation assay conducted on the most recent tumour sample available. Primary tumour or tumour from a metastatic site was tested with an investigational use only assay (IUO). The IUO is an allele-specific polymerase chain reaction (PCR) assay performed on DNA extracted from formalin-fixed paraffin-embedded (FFPE) tumour tissue. The assay was specifically designed to differentiate between the V600E and V600K mutations. Only subjects with BRAF V600E or V600K mutation positive tumors were eligible for study participation. Subsequently, all patient samples were re-tested using the bioMerieux (bMx) THxID BRAF validated assay, which has CE marking. The bMx THxID BRAF assay is an allele-specific PCR performed on DNA extracted from FFPE tumour tissue. The assay was designed to detect the BRAF V600E and V600K mutations with high sensitivity (down to 5 % V600E and V600K sequence in a background of wild-type sequence using DNA extracted from FFPE tissue). Non-clinical and clinical studies with retrospective bi-directional Sanger sequencing analyses have shown that the test also detects the less common BRAF V600D mutation and V600E/K601E mutation with lower sensitivity. Of the specimens from the non-clinical and clinical studies (n = 876) that were mutation positive by the THxID BRAF assay and subsequently were sequenced using the reference method, the specificity of the assay was 94 %''.

2.5.3. Conclusions on the clinical efficacy

In conclusion, a clinically relevant effect of dabrafenib has been shown in the patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Regarding the primary endpoint PFS, the magnitude of the observed effect (HR=0.37) is considered clinically significant. Secondary efficacy endpoints also consistently showed antitumoral activity of clinical relevance of dafrafenib in this patient population. The PFS results were very consistent and robust in all sensitivity and subgroup analyses to support on overall favourable conclusion.

2.6. Clinical safety

The safety analyses are based on data from an integrated safety population of 578 subjects with melanoma, treated with 150 mg BID dabrafenib monotherapy. The integrated safety population is merged from five clinical studies: one pivotal phase 3 (BREAK-3) and four supportive studies (BREAK 2, BREAK-MB, BRF-113220 and BRF-112680). In addition, serious adverse events (SAEs) were evaluated across the five clinical studies, as well as studies BRF113771, BRF115252, BRF113928 and BRF114144.

Patient exposure

Summary of exposure and baseline demographic characteristics is summarised in the following tables.

Table 24 Summary of exposure to dabrafenib in BREAK-3 (safety population) and across dabrafenib studies (integrated safety population)

	BREAK-3		Total Dabrafenib Monotherapy (N=578)
	DTIC (N=59)	Dabrafenib[a] (N=187)	
Dabrafenib daily dose (mg) or DTIC dose intensity (mg/m^2/week)			
Mean	311.63	284.92	284.77
SD	34.23	33.54	34.95
Median	332.00	300.00	300.00
Minimum	204.00	118.00	90.90
Maximum	350.00	300.00	426.20[b]
Time on study treatment (months)			
Minimum	0.69	0.13	0.07
1st quartile	na	4.11	2.99
Median	2.79	4.93	4.62
3rd quartile	na	6.14	6.37
Maximum	9.89	10.28	15.97
Proportion of subjects on study treatment for specific time intervals (months)	**Number (%) of Subjects**		
<3	32 (54)	33 (18)	145 (25)
3-6	21 (36)	105 (56)	272 (47)
>6-12	6 (10)	49 (26)	157 (27)
>12	0	0	4 (<1)

a. Includes 1 subject who was randomized to DTIC and mistakenly received dabrafenib throughout study participation due to a site error. Exceeds daily therapeutic dose under development due to 1 subject in BRF112680 who was dose-escalated to 300 mg BID dabrafenib following disease progression, which was allowed per the study protocol.

Table 25 Demographic characteristics for BREAK-3 (Safety Population) and across Dabrafenib studies(ISS Safety Population)

Characteristic	BREAK-3		Total Dabrafenib Monotherapy (N=578)
	DTIC (N=59)	Dabrafenib (N=187)	
Age (yrs)			
Mean	52.1	53.3	53.0
SD	14.47	13.71	14.04
Median	51.0	53.0	53.0
Minimum	21	22	18
Maximum	82	93	93
Age group (yrs), n (%)			
<65	47 (80)	147 (79)	453 (78)
65-74	8 (14)	28 (15)	93 (16)
75-84	4 (7)	11 (6)	29 (5)
≥75	4 (7)	12 (6)	32 (6)
≥85	0	1 (<1)	3 (<1)
Sex, n (%)			
Female	25 (42)	75 (40)	226 (39)
Male	34 (58)	112 (60)	352 (61)
Ethnicity, n (%)			
Hispanic or latino	0	7 (4)	17 (3)
Not hispanic or latino	59 (100)	180 (96)	556 (96)
Missing	0	0	5 (<1)

Adverse events

An overview of adverse events in the pivotal study and in the integrated safety population is summarized in table 26.

Table 26 AEs in the pivotal study and in the integrated safety population

	Number (%) of Subjects		
	BREAK-3		Total Dabrafenib Monotherapy (N=578)
	DTIC (N=59)	Dabrafenib (N=187)	
Any AE	**54 (92)**	**185 (99)**	**554 (96)**
AEs related to study treatment	43 (73)	164 (88)	499 (86)
AEs leading to permanent discontinuation of study treatment	2 (3)	5 (3)	10 (2)
AEs leading to dose reduction	10 (17)	34 (18)	80 (14)
AEs leading to dose interruption/delay	16 (27)	51 (27)	170 (29)
Any SAE	13 (22)	43 (23)	150 (26)
SAEs related to study treatment	2 (3)	28 (15)	96 (17)
Fatal SAEs	0	1 (<1)	5 (<1)

A summary of grade 3 or grade 4 adverse events reported by at least 2% of subjects on either treatment arm by maximum grade in the BREAK-3 safety population is presented in Table 27.

Table 27 Summary of grade 3 or grade 4 adverse events reported by at least 2% of subjects on either treatment arm by maximum grade in the BREAK-3 safety population

Preferred term	GSK2118436 (N=187)			DTIC (N=59)		
	Grade 3 n (%)	Grade 4 n (%)	Total n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Any event	**55 (29)**	**7 (4)**	**185 (99)**	**16 (27)**	**8 (14)**	**54 (92)**
Pyrexia	6 (3)	0	52 (28)	0	0	6 (10)
Palmar-plantar erythrodysaesthesia syndrome	4 (2)	0	37 (20)	0	0	1 (2)
Asthenia	1 (<1)	0	33 (18)	1 (2)	0	9 (15)
Back pain	5 (3)	0	22 (12)	0	0	4 (7)
Constipation	2 (1)	1 (<1)	21 (11)	0	0	8 (14)
Decreased appetite	0	0	16 (9)	2 (3)	0	5 (8)
Hyperglycaemia	3 (2)	0	8 (4)	1 (2)	0	1 (2)
Abdominal pain	1 (<1)	0	7 (4)	0	1 (2)	8 (14)
Anaemia	1 (<1)	0	7 (4)	1 (2)	1 (2)	7 (12)
Alanine aminotransferase increased	3 (2)	0	7 (4)	0	0	0
Hypophosphataemia	4 (2)	0	7 (4)	0	0	0
Squamous cell carcinoma	6 (3)	0	7 (4)	0	0	0
Anxiety	1 (<1)	0	6 (3)	1 (2)	0	5 (8)
Hypertension	1 (<1)	0	6 (3)	1 (2)	0	2 (3)
Gamma-glutamyltransferase increased	3 (2)	0	4 (2)	1 (2)	0	2 (3)
Hepatic pain	1 (<1)	0	3 (2)	0	1 (2)	1 (2)
Squamous cell carcinoma of skin	3 (2)	0	3 (2)	0	0	0
Neutropenia	1 (<1)	0	2 (1)	4 (7)	4 (7)	10 (17)
Bone pain	0	0	2 (1)	2 (3)	0	2 (3)
Pain	0	0	2 (1)	0	1 (2)	2 (3)
Leukopenia	0	0	1 (<1)	2 (3)	0	6 (10)
Thrombocytopenia	1 (<1)	0	1 (<1)	1 (2)	2 (3)	5 (8)
Fall	0	0	1 (<1)	1 (2)	0	1 (2)
Gastrointestinal infection	0	0	1 (<1)	1 (2)	0	1 (2)
Haematuria	1 (<1)	0	1 (<1)	1 (2)	0	1 (2)
Pulmonary embolism	1 (<1)	0	1 (<1)	1 (2)	0	1 (2)
Depression	0	0	0	1 (2)	0	2 (3)
Melaena	0	0	0	1 (2)	0	2 (3)
Neutrophil count decreased	0	0	0	1 (2)	0	2 (3)
White blood cell count decreased	0	0	0	1 (2)	0	2 (3)
Angina pectoris	0	0	0	1 (2)	0	1 (2)
Febrile neutropenia	0	0	0	0	1 (2)	1 (2)
Hyperkalaemia	0	0	0	1 (2)	0	1 (2)
Lymphocyte count abnormal	0	0	0	1 (2)	0	1 (2)
Neutrophil count abnormal	0	0	0	1 (2)	0	1 (2)
Platelet disorder	0	0	0	1 (2)	0	1 (2)
Sepsis	0	0	0	1 (2)	0	1 (2)
Splenic rupture	0	0	0	0	1 (2)	1 (2)
White blood cell count abnormal	0	0	0	1 (2)	0	1 (2)

A summary of adverse events considered related to study treatment in at least 10% of subjects in BREAK-3 (safety population) or across dabrafenib studies (total Pooled safety population) is presented in table 28 below.

Table 28 Summary of adverse events considered related to study treatment in at least 10% of subjects in BREAK-3 (safety population) or across dabrafenib studies (total Pooled safety population)

Preferred term	Number (%) of Subjects		
	BREAK-3		Total Dabrafenib Monotherapy (N=578)
	DTIC (N=59)	Dabrafenib (N=187)	
Any event	**43 (73)**	**164 (88)**	**499 (86)**
Hyperkeratosis	0	63 (34)	150 (26)
Fatigue	13 (22)	32 (17)	108 (19)
Skin papilloma	0	40 (21)	105 (18)
Arthralgia	0	30 (16)	100 (17)
Pyrexia	0	28 (15)	97 (17)
Rash	0	29 (16)	97 (17)
Alopecia	1 (2)	37 (20)	94 (16)
Headache	2 (3)	32 (17)	77 (13)
Nausea	21 (36)	18 (10)	74 (13)
PPE syndrome	1 (2)	35 (19)	74 (13)
Myalgia	0	16 (9)	57 (10)
Asthenia	7 (12)	26 (14)	40 (7)
Vomiting	12 (20)	8 (4)	36 (6)
Neutropenia	9 (15)	2 (1)	11 (2)

Adverse drug reactions (ADRs) in the integrated safety population are summarised in the following table. The most frequently occurring ADRs (≥ 15 %) reported with dabrafenib were hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, papilloma, alopecia, rash and vomiting.

Table 29 Adverse reactions reported in the integrated safety population

System Organ Class	Frequency (all grades)	Adverse Reactions
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Very common	Papilloma
	Common	Cutaneous squamous cell carcinoma
	Common	Seborrhoeic keratosis
	Common	Acrochordon (skin tags)
	Common	Basal cell carcinoma
	Uncommon	New primary melanoma
Immune system disorders	Uncommon	Hypersensitivity
	Uncommon	Panniculitis
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Hypophosphataemia
	Common	Hyperglycaemia
Nervous system disorders	Very common	Headache
Eye disorders	Uncommon	Uveitis
Respiratory, thoracic and mediastinal disorders	Very common	Cough
Gastrointestinal disorders	Very common	Nausea
	Very common	Vomiting

System Organ Class	Frequency (all grades)	Adverse Reactions
	Very common	Diarrhoea
	Common	Constipation
	Uncommon	Pancreatitis
Skin and subcutaneous tissue disorders	Very common	Hyperkeratosis
	Very common	Alopecia
	Very common	Rash
	Very common	Palmar –plantar erythrodysaesthesia syndrome
	Common	Dry skin
	Common	Pruritus
	Common	Actinic keratosis
	Common	Skin lesion
	Common	Erythema
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
	Very common	Myalgia
	Very common	Pain in extremity
Renal and urinary disorders	Uncommon	Renal failure, acute renal failure
	Uncommon	Nephritis
General disorders and administration site conditions	Very common	Pyrexia
	Very common	Fatigue
	Very common	Chills
	Very common	Asthenia
	Common	Influenza-like illness
Investigations	Common	LVEF decrease
	Uncommon	QT prolongation

Certain AEs which were identified as events of special interest because of their presumed relationship to BRAF- or other kinase inhibitors observed in clinical or preclinical studies, or due to the discovery of these AEs in early studies of dabrafenib are described in some detail below.

Pyrexia

Pyrexia was reported in 28% of the patients in the pivotal study and in 27% in the integrated safety population; the events occurred rather early (median 3 weeks) and lasted less than 5 days. Most of the events were considered drug-related (64%). Six per cent of the events were grade 3 (no grade 4), and 98% of the events were resolved. Thirty-four per cent of patients reported with pyrexia required dose interruption, and 16% needed dose reduction.

In 1 % of patients in clinical trials, serious non-infectious febrile events were defined as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency or pre-renal origin in subjects with normal baseline renal function. The onset of these serious non-infectious febrile events was typically within the first month of therapy. Patients with serious non-infectious febrile events responded well to dose interruption and/or dose reduction and supportive care.

Cutaneous SCC and keratoacanthomas

In the integrated safety population a total of 52 (9%) of the subjects had a total of 89 events of cutaneous squamous cell carcinomas (cuSCC), Bowen´s disease ("squamous cell carcinoma in situ") or keratoacanthoma. Approximately 70% of events occurred within the first 12 weeks of treatment with a median time to onset of 8 weeks. Ninety-six per cent of patients who developed cuSCC continued on treatment without dose modification.

Treatment-emergent malignancies

Three subjects with non-epithelial treatment-emergent malignancies (mycosis fungoides, AML, and myelodysplastic syndrome [MDS]) were identified. There was a reasonable possibility that the mycosis fungoides may have been caused by dabrafenib. Both AML and MDS have been assessed by the investigator as unrelated to dabrafenib.

Basal cell carcinoma was reported in five patients (3%) in the pivotal study and in 13 subjects of the integrated safety population.

Renal failure

Overall, four subjects (<1%) in the integrated dabrafenib safety population experienced AEs of renal failure. Two subjects had events reported as serious. One SAE was considered related to study treatment. Three of the four events occurred during the first 12 weeks of treatment (median time to onset was five weeks). All events were managed with dabrafenib dose-modification. Observed cases were generally associated with pyrexia and dehydration. No cases of renal failure were reported in the pivotal study. Renal failure due to pyrexia-associated pre-renal azotaemia or granulomatous nephritis was uncommon. In the pooled dabrafenib population, 6% subjects across studies experienced at least one increase in serum creatinine as compared with baseline, which was similar to the incidence in the pivotal study.

Uveitis/Iritis

Uveitis/Iritis has been reported in five cases in the integrated safety population (one case of iritis and 4 cases of uveitis). Four of the cases were considered related to study treatment by the investigator. The cases were manageable without permanent discontinuation of dabrafenib. In the pivotal study one case of iritis was reported. In total, eye disorders were reported in 9% of the patients in the integrated safety population, the most common events except uveitis were vision blurred (14 cases), dry eye (7 cases) and ocular hyperaemia (5 cases).

Neutropenia

In the integrated safety population, a total of six subjects (1%) experienced Grade 3 or Grade 4 events of neutropenia. Five of these were considered study drug-related by the investigator, and all events were reported as resolved at study cut-off. All events were confounded by prior and/or concurrent treatment with other drugs known to cause neutropenia. None of the events were associated with febrile neutropenia. Two subjects had pancytopenia attributable to multiple ethiologies. Neutropenia was a common AE on DTIC, reported for 17% of subjects overall, and the majority of these cases (8 out of 10 subjects) were high-grade events.

Testicular toxicity

Testicular toxicity was identified in preclinical studies characterized by seminferous tubule degeneration, spermatid depletion/retention and observed below human exposure. Two events of testicular pain and one case of testicular swelling were reported out of in total 30 events of "Reproductive system and breast disorders". The most common reproductive events were menstrual irregularities, furthermore two cases of galactorrea/breast discharge and two cases of benign prostate hyperplasia were reported.

Pancreatitis

Two cases of pancreatitis were reported in the integrated safety population.

Cardiac events

Due to preclinical data of potential cardiac valve abnormalities caused by dabrafenib, ECG surveillance was performed in all clinical studies. Valvular abnormalities were therefore monitored as AEs of special interest. Cardiac abnormalities including valvular disorders were reported in total 10% in the pivotal study. Two cases of mitral valve incompetence, one case of mitral valve disease and one case of tricuspid valve disease was reported in three patients. One case was a worsening of previously existing valvular disease. In two cases the investigators considered a relationship with dabrafenib. In total cardiac disorders were reported in 8% of the patients in the integrated safety population, the most common events being tachycardia (2%) atrial fibrillation (2%) and palpitations (2%).

Abnormal ejection fraction

In BREAK-3 an absolute reduction in LVEF of at least 10% from baseline and below the lower limit of normal (LLN), was observed in 2% of the subjects. In the DTIC arm no subjects were registered with these values.

In the integrated safety population a total of 6 (1%) of the patients were observed with a decreased LVEF. All these cases were Grade 2 in severity, except for one Grade 3 event in a subject with baseline ischemia and cardiomyopathy who did not meet protocol eligibility criteria.

Arthralgia

Arthralgia was reported very commonly in clinical trials with dabrafenib (25 %). These cases were mainly grade 1 and 2 in severity with grade 3 occurred uncommonly (< 1 %) and no grade 4 occurrences were reported.

QT-interval

In the Break-3 study no subjects in either arm had a QTcB value greater than 500 msec. Six subjects (4%) in the dabrafenib arm and two subjects (5%) in the DTIC arm had a post baseline QTcB value greater than 480 msec, but less than 500 msec.

Most subjects in the integrated safety population (74%) maintained a machine-read QTcB <450 ms during study participation. Increases to >480 ms occurred in 2% of the subjects. One subject in the integrated safety population experienced a QTcB > 500 ms. Three subjects (2%) in the dabrafenib-arm and one subject (3%) in the DTIC-arm had a change from baseline in QTcB of greater than 60 msec. The subjects in the dabrafenib arm with a change from baseline in QTcB of greater than 60 msec had a baseline QTcB less than 400 msec at baseline and did not have a post-baseline QTcB exceeding 480 msec. Across dabrafenib studies, subjects who experienced an increase in QTcB of 31 to 60 ms or >60 ms were 16% and 3%, respectively.

Based on an exposure-QTc analysis performed with data from the FTIH study BRF112680, dabrafenib concentrations showed no apparent potential to alter the manually read QTc interval. A similar exposure analysis with metabolite concentrations showed a positive slope with a maximum change in population-corrected QTc of ≤5.5 msec at the mean maximum observed plasma concentration (C_{max}) observed with 150 mg or 300 mg BID dabrafenib.

Hypophosphataemia

Hypophosphataemia has been reported commonly in clinical trials with dabrafenib (7%). Approximately half of these (4%) occurrences were Grade 3 in severity.

Serious adverse event / deaths / other significant events

Deaths

At the time of clinical data cut-off for BREAK-3, 21 subjects (11%) randomized to dabrafenib and 9 subjects (15%) randomized to DTIC had died (Table 30).

All deaths were attributed to the disease under study, with the exception of one death in the dabrafenib arm in the BREAK-3 study and four deaths in the integrated safety population.

Table 30 Summary of deaths in BREAK-3 by randomized treatment group (safety population) and across dabrafenib Studies (total safety population)

	Number (%) of Subjects		
	BREAK-3[a]		Total Dabrafenib Monotherapy (N=578)
	DTIC (N=59)	Dabrafenib (N=187)	
Subject status			
Dead	9 (15)[c]	21 (11)	141 (24)
Alive at last contact, follow-up ended[b]	2 (3)	5 (3)	56 (10)
Alive at last contact, follow-up ongoing	48 (81)	161 (86)	381 (66)
Alive at crossover	28 (47)	0	0
Primary cause of death			
Disease under study	9 (15)[c]	20 (11)	137 (24)
Other	0	1 (<1)[d]	2 (<1)[e]
Unknown	0	0	2 (<1)[f]
Time to death from last dose			
≤30 days	4 (7)	8 (4)	67 (12)
>30 days	5 (8)	13 (7)	74 (13)

a. Results are presented by randomized treatment group. b. Subject withdrew consent for follow-up or was lost to follow-up .c.Includes 4 subjects who died due to disease progression after receiving dabrafenib in the cross-over phase of BREAK-3. d.Subject with elective euthanasia. e. Subject with elective euthanasia in BREAK-3 and Subject with disease progression in BREAK-MB. f. 1 subject in BREAK-MB and 1 subject in BREAK-2. Since the clinical cut-off dates for these studies, additional information received from the investigator indicated the primary cause of death in both cases was disease progression.

Serious adverse events (SAEs)

A summary of serious adverse events occurred in at least 2 subjects in the pivotal study or in the integrated safety population is presented in Table 31.

Table 31 Summary of serious adverse events in at least 2 subjects in BREAK-3 (safety population) or across dabrafenib studies (total safety population)

Preferred term	Number (%) of Subjects		
	BREAK-3		Total Dabrafenib Monotherapy (N=578)
	DTIC (N=59)	Dabrafenib (N=187)	
Any event	13 (22)	43 (23)	150 (26)
Squamous cell carcinoma	0	7 (4)	32 (6)
Pyrexia	0	7 (4)	27 (5)
Squamous cell carcinoma of skin	0	3 (2)	9 (2)
Atrial fibrillation	0	2 (1)	7 (1)
Hypotension	0	2 (1)	7 (1)
Anaemia	1 (2)	1 (<1)	6 (1)
Vomiting	1 (2)	2 (1)	6 (1)
Chills	0	1 (<1)	6 (1)
Headache	0	0	6 (1)
Nausea	1 (2)	1 (<1)	5 (<1)
Basal cell carcinoma	0	1 (<1)	5 (<1)
Haemorrhage intracranial	0	0	5 (<1)
Syncope	0	1 (<1)	5 (<1)
Ejection fraction decreased	0	2 (1)	4 (<1)
Fatigue	0	0	4 (<1)
Malignant melanoma	0	3 (2)	4 (<1)
Pleural effusion	0	1 (<1)	4 (<1)
Pulmonary embolism	1 (2)	1 (<1)	3 (<1)
Cerebral haemorrhage	0	0	3 (<1)
Dehydration	0	1 (<1)	3 (<1)
Hyponatraemia	0	1 (<1)	3 (<1)
Pneumonia	0	0	3 (<1)
Abdominal pain	2 (3)	0	2 (<1)
Neutropenia	1 (2)	0	2 (<1)
Sepsis	1 (2)	0	2 (<1)
Aphasia	0	0	2 (<1)
Confusional state	0	0	2 (<1)
Deep vein thrombosis	0	0	2 (<1)
Hypophosphataemia	0	1 (<1)	2 (<1)
Influenza like illness	0	1 (<1)	2 (<1)
Intracranial tumour haemorrhage	0	0	2 (<1)

Localised infection	0	1 (<1)	2 (<1)
Muscular weakness	0	1 (<1)	2 (<1)
Non-cardiac chest pain	0	0	2 (<1)
Pancreatitis	0	1 (<1)	2 (<1)
Pancytopenia	0	0	2 (<1)
Presyncope	0	1 (<1)	2 (<1)
Renal failure acute	0	0	2 (<1)
Thrombocytopenia	0	0	2 (<1)
Urosepsis	0	0	2 (<1)

A summary of serious adverse events after the respective data cut-off dates through March 2012, from all five clinical studies in the pooled safety population of dabrafenib, as well as from three additional studies (BRF115252, BRF113928 and BRF114114), is presented in Table 32.

Table 32 Serious adverse events reported in dabrafenib clinical studies from CSR Data cut-off through 30 March 2012 (56 patients)

System Organ Class	Total Events[a]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	31
General disorders and administration site conditions	12[b]
Nervous system disorders	10
Cardiac disorders	8
Infections and infestations	6
Gastrointestinal disorders	5
Blood and lymphatic system disorders	4
Psychiatric disorders	4
Vascular disorders	4
Investigations	3
Injury, poisoning and procedural complications	2
Metabolism and nutrition disorders	2
Renal and urinary disorders	2
Hepatobiliary disorders	1
Musculoskeletal and connective tissue disorders	1
Respiratory, thoracic and mediastinal disorders	1
Skin and subcutaneous tissue disorders	1
Total SAEs	**97**

a. Includes events in a total of 56 subjects from BREAK-3, BREAK-MB, BREAK-2, BRF113220, and BRF112680 and BRF113771 (cut-off date 25 February 2012) from the respective CSR cut-off dates through 30 March 2012.

b. Includes 8 cases of pyrexia, of which 4 were considered related to study treatment.

Laboratory findings

In the pivotal study more haematologic abnormalities were reported in the DTIC group than in the dabrafenib group. In the dabrafenib group there was one patient (<1%) with grade 4 lymphopenia, 6 patients (3%) with lymphopenia grade 3 and one patient (<1%) with grade 3 neutropenia. In the integrated safety population the frequencies was slightly higher than in the pivotal study.

Neutropenia, leukopenia, and thrombocytopenia all occurred at a greater frequency and severity in DTIC-treated subjects as compared with those receiving dabrafenib (both in BREAK-3 and across dabrafenib studies). Febrile neutropenia was reported as an AE only in DTIC-treated subjects.

The most common laboratory finding in the pivotal study were as follows: hyperglycemia in 50% of the patients (grade 3 in 12 patients [6%]), hypophosphatemia in 37% of the patients (grade 3 in 10 patients [5%], grade 4 in one patient) increase in alkaline phosphatase in 19% of the patients (no grade 3-4), increase in ALT in 11% of the patients (grade 3 in 2 patients [1%], no grade 4), increase in AST in 8% of the patients (grade 3 in 1 patients [<1%], no grade 4), and hyponatremia in 8% of the patients (grade 3 in 4 patients [2%], no grade 4). In the integrated safety population the results were similar (hyperglycemia 48%, hypophospatemia 35%, ALP 22%, ALT 16%, AST 13%. The findings were similar in the DTIC with regards to hyperglycemia (43%) and increase in AST (8%) but with regards to hypophosphatemia the incidence was lower (14%) and for ALT the incidence was higher (22%). There were no cases fulfilling criteria for Hy´s law in either the pivotal study or in the integrated safety population.

A summary of worse-case on-therapy increases in machine-read corrected QT interval on electrocardiogram with Bazett's correction (QTcB) was performed using data from BREAK-3, BREAK-MB, and BREAK-2. No instance of QTcB >500 ms was observed and the proportion of subjects with QTcB prolongation of >60 ms was 3% in this safety population. An increase in QTcB of 31 – 60ms was observed in 16% of the patients. Furthermore in one subject in the FTIH study who received a total daily dose on of 900 mg by mistake a QTcF of 505 ms was reported. One case with QT >500 ms was noted in the safety update.

Safety in special populations

AEs reported more frequently in older subjects (≥65) as compared with younger (<65) were hyperkeratosis (34% vs. 27%), fatigue (30% vs. 23%), skin papilloma (29% vs. 17%), chills (21% vs. 9%), constipation (16% vs. 7%), seborrheic keratosis (15% vs. 5%), peripheral oedema (13% vs. 5%), actinic keratosis (12% vs. 6%), weight decreased (10% vs. 4%), and dyspnoea (9% vs. 4%). Conversely, an increased frequency of alopecia (21% vs. 14%) and PPE syndrome (15% vs. 9%) were reported in subjects <65 years old as compared with ≥65 (data not shown). Thirty two subjects in the integrated safety population were ≥75 years old and only 3 subjects were >85 years old. Based on these numbers, limited safety conclusions can be drawn.

No important gender–related safety differences were detected in the integrated safety population. Overall, rates of AEs, SAEs, and AEs leading to dose modifications were similar in both male and female subgroups. The frequency of Grade 3 and Grade 4 events was also similar between subgroups. There were 4 (2%) fatal SAEs in females and 1 (<1%) in males.

Safety related to drug-drug interactions and other interactions

There were no safety studies submitted for drug-drug interaction.

Discontinuation due to adverse events

Five patients (3%) in the pivotal study and 10 patients (2%) in the integrated safety population had AEs leading to permanent discontinuations.

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The median treatment duration in patients receiving dabrafenib was 4.9 months in the pivotal BREAK-3 study, whereas median treatment duration was 4.6 months across all studies. Although 4 patients in the integrated safety population were treated for more than one year, the data from patients using dabrafenib over a prolonged period is limited. Based on this, "long term safety'' included as missing information in the RMP and cumulative annual safety listings and analyses will be provided by the applicant.

The most frequently occurring ADRs (≥ 15 %) reported with dabrafenib were hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, papilloma, alopecia, rash and vomiting.

The majority of the adverse events were of grade 1-2, the dose intensity is high, about 95%, and only 5 patients (3%) in the pivotal study and 10 patients (2%) in the integrated safety population discontinued treatment due to side effects indicating the treatment is tolerable in this setting.

The most frequent SAEs in the dabrafenib group were cutaneous SCC (6%) and pyrexia (5 %). A total of 5 subjects in the integrated dabrafenib safety population experienced a Grade 5 SAE, none of which were attributed to study treatment.

Pyrexia and PPES were two of the most common reasons for dose reductions/interruptions however neither pyrexia nor PPES led to definitive treatment discontinuations. The onset of these serious non-infectious febrile events was typically within the first month of therapy. There are different proposed mechanisms for pyrexia including CNS thermoregulation via PGE2, activation of inflammation via TLR, and cytokine increase which is the currently plausible mechanism. Patients with serious non-infectious febrile events responded well to dose interruption and/or dose reduction and supportive care. A relevant precaution was included in section 4.4 of the SmPC.

Squamous epithelial carcinoma was reported in 6% and keratoacanthoma in 3% of the patients treated with dabrafenib arm in the pivotal study compared to no cases in the dacarbazine arm, skin neoplasms (squamous epithelial carcinoma (6%) and malignant melanomas (2%) were also reported as some the most common SAEs. Basal cell carcinomas were reported in 3% of the dabrafenib treated patients in the pivotal study compared to no DTIC treated patients. However these events did not lead to permanent treatment discontinuations. With examinations that could lead to excisions, these events are manageable. Relevant Information was included in the SmPC.

There is a biological mechanism described in BRAF inhibition with a paradoxical RAS activation that can lead to an increase in squamous epithelial malignancies, this is relevant both in cutaneous squamous epithelial carcinomas but also for non-skin squamous epithelial carcinomas. There are indications that other malignancies such as malignant melanocytic tumours and also chronic myeloid leukaemias may also show accelerated growth. Cases of RAS-associated malignancies have been reported, both with another BRAF inhibitor (Chronic myelomonocytic leukemia and non-cutaneous SCC of the head and neck) and with dabrafenib when administered in combination with the MEK inhibitor, trametinib (colorectal cancer, pancreatic cancer). Further information will be collected in the adjuvant study BRF115532 (a phase III randomized double blinded study of dabrafenib in combination with trametinib versus two placebos in the adjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection). A Phase III, randomized, double-blinded study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo as first-line therapy in subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutationpositive cutaneous melanoma will also address this specific safety issue. Appropriate wording in section 4.4 of the SmPC has been implemented.

New primary melanomas have been reported in clinical trials with dabrafenib. Cases were managed with excision and did not require treatment modification. Monitoring for skin lesions should occur as described for cutaneous squamous cell carcinoma.

The majority of cardiac events were reported in dabrafenib and not in DTIC treated patients. The imbalance in the group size and the length of treatment could be an explanation however as there also are preclinical findings this should be further addressed. Furthermore the impact of dabrafenib in reduced cardiac function is unkown as these patients were excluded from the studies. An ongoing QTc study (BRF113773) designed to evaluate the effect of repeat oral dosing of dabrafenib on cardiac repolarization in subjects with solid tumours will elucidate the risk of QTc prolongation. The study is included in the RMP and a relevant precaution was included in section 4.4 of the SmPC.

Renal failure due to causes other than pyrexia-associated pre-renal azotaemia (e.g. granulomatous nephritis) was uncommon; however dabrafenib has not been studied in patients with baseline renal insufficiency. Caution should be used in this setting (see SmPC section 4.8).

Five cases of uveitis/iritis were reported in the integrated safety population (one case of iritis and 4 cases of uveitis). Patients should be routinely monitored for visual signs and symptoms (such as, change in vision, photophobia and eye pain) while on therapy (see SmPC section 4.4).

The prevalence of photo-sensitivity in the dabrafenib safety population is low (2% overall) and the safety database is still small. Therefore a clinical relevance cannot be ruled out. However there are preclinical signs and due to the severity of this condition (patients may get burned in daylight) photosensitivity has been added as a potential risk in the RMP.

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

In total 125 patients in the integrated safety population were aged 65 or more, this is about 20% of the population about 6% were older than 75 years. About 40% were women in the integrated safety population. No major differences with regards to sex or age were detected. Dabrafenib has been studied almost exclusively in Caucasians, consequently the information regarding safety in other

populations is very limited. “Non-White population” has been included as missing information in the RMP.

There is no specific treatment for an overdose of dabrafenib. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary (see SmPC section 4.9).

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

2.6.2. Conclusions on the clinical safety

In summary, the safety profile of dabrafenib seems consistent across the pooled safety population. The overall toxicity profile of dabrafenib seems acceptable and SAEs known to be related to dabrafenib treatment are mostly manageable.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.8. Risk Management Plan

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

PRAC Advice

The RMP is acceptable.

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

- **Safety concerns**

Summary of safety concerns	
Main identified risks	• Cutaneous SCC (cuSCC) • New primary melanoma • Non-cutaneous secondary/recurrent malignancies • Pyrexia • Pre-renal and Intrinsic Renal failure • Hypersensitivity • Pancreatitis • Uveitis • Palmar-Plantar Erythrodysesthesia Syndrome (PPES)
Main potential risks	• Testicular Toxicity • Increased risk for Grade 3 or 4 AEs, SAEs or dose adjustments in elderly

Summary of safety concerns	
	population (≥65 years) • Off-label use in resectable/resected melanoma (adjuvant treatment), non-melanoma tumours harbouring a BRAFV600-mutation, in combination with other anti-cancer agents, or when non-validated tests are used • Paediatric effects • Potential for QT Prolongation • Drug-drug interactions • Non-specific cardiac toxicity • Hyperglycaemia • Photosensitivity
Additional information to be provided	• Use in patients with reduce cardiac function or symptomatic NYHA Class II, III, or IV heart failure (NYHA functional classification system) • Safety in patients with severe renal impairment • Safety in patients with moderate to severe hepatic impairment • Use in Non-White population • Developmental toxicity and risks in breast-feeding • Risks in patients with ECOG 2-4 • Rare adverse reactions • Long-term treatment • Use in patients with baseline QTc ≥480 msec; history of acute coronary syndrome (including unstable angina), coronary angioplasty, stenting or cardiac arrhythmias (except sinus arrhythmia) within the past 24 weeks; and abnormal cardiac valve morphology (moderately abnormal or worse)

The safety specification is endorsed.

- **Pharmacovigilance plans**

Activity/Study title	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
In vivo interaction study with an OATP1B1/3 substrate (category 3)	To evaluate the effect of single and repeat dose dabrafenib on the single dose pharmacokinetics of an OATP1B1/1B3 substrate such as rosuvastatin and of CYP3A4 substrate	Drug-drug interaction	Planned start 1Q2014	Final report projected in 1Q 2017

Activity/Study title	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
	midazolam			
BRF113773: QTc Study (category 3)	To evaluate the effect of dabrafenib on ECG parameters, in particular cardiac repolarization	QT prolongation	Started; Planned finish 1Q2015	Final report 4Q2015
BRF113771: Four-part Pharmacokinetic Study (category 3)	To evaluate the effects of repeat dose dabrafenib on the single dose pharmacokinetics of warfarin, the effects of repeat dose oral ketoconazole and oral gemfibrozil on the repeat dose pharmacokinetics of dabrafenib, and the repeat dose pharmacokinetics of dabrafenib in subjects with BRAF mutant solid tumors.	Drug-drug interaction	Started; finished 1Q2013	Final report 2Q2013
BRF115532 (COMBI-AD) Phase III Adjuvant Study (category 3)	A phase III randomized double blind study of dabrafenib in combination with trametinib versus two placebos in the adjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection	Long-term safety with focus on non-cutaneous malignancies	Started; primary analysis finish 4Q2015	Primary study report projected 1Q2016
200072: Drug-drug interaction study of the effects of a strong CYP3A4 inducer (e.g. rifampin) and a pH-altering agent (e.g., proton pump inhibitor) on dabrafenib (category 3)	To evaluate the effect of repeat dose of rifampin, a strong CYP3A4 inducer, and of a pH altering agent (i.e., proton pump inhibitor) on the repeat dose pharmacokinetics of dabrafenib.	Drug-drug interaction	Planned start 4Q2013	Final report 4Q2016
In vitro organic anion transporter polypeptide	To obtain information on in vitro hepatocyte	Drug-drug interaction	Planned start 3Q2013	Final report 4Q2013

Activity/Study title	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
substrate assay (category 3)	uptake studies for dabrafenib, hydroxy-dabrafenib, carboxydabrafenib, and desmethyl-dabrafenib. For those compounds which demonstrate active uptake, additional in vitro studies to interrogate OATP1B1 and OATP1B3 substrate status will be conducted where appropriate.			
MEK115306 (COMBI-D) Phase III Study (category 3)	A Phase III, randomized, double-blinded study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo as first-line therapy in subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma	Long-term safety with focus on non-cutaneous malignancies	Started; study finish projected 2Q2015	Primary study report projected 1Q2014
BRF113683 (BREAK-3) (category 3)	A Phase III randomized, open-label study comparing dabrafenib to DTIC in previously untreated subjects with BRAF mutation positive advanced (Stage III) or metastatic (Stage IV) melanoma.	Long-term safety with focus on non-cutaneous malignancies	Started; study finish 2Q2014	Final report projected 4Q2014

The Pharmacovigilance Plan is endorsed.

- **Risk minimisation measures**

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
cuSCC	• *Warning in product labelling* • *ADR in product labelling* • *Guidance for management in protocols, product labelling* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.* • *Information for patients in PIL*	*None*
New primary melanoma	• *Warning in product labelling* • *ADR in product labelling* • *Guidance for management in protocols, product labelling* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.* • *Information for patients in PIL*	*None*
Non-cutaneous secondary / recurrent malignancies	• *Warning in product labelling* • *Described in section 4.8* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.* • *Information on monitoring for patients in PIL*	*None*
Pyrexia	• *Warning in product labelling* • *ADR in product labelling* • *Guidance for management in protocols, product labelling* • *Information for patients in PIL* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician*	*None*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	experienced in the administration of anti-cancer medicinal products.	
Pre-renal and intrinsic Renal failure	• *Referred to in warning for pyrexia in product labelling* • *Warning in product labelling* • *ADR in product labelling* • *Guidance for pyrexia management in protocols, product labelling* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.* • *Information for patients in PIL*	*None*
Hypersensitivity	• *Contraindication in product labelling* • *ADR in product labelling* • *Information for patients in PIL* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.*	*None*
Pancreatitis	• *Warning in product labelling* • *ADR in product labelling* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.* • *Information for patients in PIL*	*None*
Uveitis	• *Warning in product labelling* • *ADR in product labelling* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the*	*None*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	administration of anti-cancer medicinal products. • *Information for patients in PIL*	
PPES	• *ADR in product labelling* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.* • *Information for patients in PIL*	*None*
Testicular Toxicity	• *Information in product labelling* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products*	*None*
Increased risk for Grade 3 and 4 AEs, SAEs and dose adjustment in elderly population (≥65 years)	• *Information in product labelling* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.*	*None*
Off-label use in resectable/ resected melanoma (adjuvant treatment), in non-melanoma tumours harbouring a BRAF V600-mutation, use in combination with other anticancer agents, or when non-validated tests are used	• *Information in product labelling* • *Information for patients in PIL* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.*	*None*
Paediatric effects	• *Information in product labelling* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of*	*None*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	anti-cancer medicinal products.	
Drug-drug interaction	• *Warning in product labelling* • *Additional information in product labelling* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.* • *Information for patients in PIL*	*None*
Non-specific cardiac toxicity	• *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products*	*None*
Photosensitivity	• *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.*	*None*
Hyperglycaemia	• *ADR in product labelling* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.*	*None*
Potential for QT Prolongation	• *Warning in product labelling* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.*	*None*
Use in patients with reduced cardiac function or symptomatic NYHA Class II, III, or IV heart failure	• *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the*	*None*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
(NYHA functional classification system)	*administration of anti-cancer medicinal products.*	
Safety in patients with severe renal impairment	• *Information in product labelling* • *Information in the PIL* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.*	*None*
Safety in patients with moderate to severe hepatic impairment	• *Information in product labelling* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.*	*None*
Non-White population	• *Statement in product labelling that there are insufficient data to evaluate the potential effect of race on dabrafenib pharmacokinetics* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.*	*None*
Developmental toxicity and risks in breast-feeding	• *Information in product labelling* • *Information for patients in PIL* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.*	*None*
Use in patients with ECOG 2-4	• *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of*	*None*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	anti-cancer medicinal products.	
Rare adverse reactions	• *Ongoing evaluation of adverse events in patients* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.*	*None*
Long-Term Treatment	• *Ongoing evaluation of adverse events in patients* • *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products*	*None*
Use in patients with baseline QTc ≥480 msec; history of acute coronary syndrome (including unstable angina), coronary angioplasty, stenting, or cardiac arrhythmias (except sinus arrhythmia) within the past 24 weeks; and abnormal cardiac valve morphology (moderately abnormal or worse)	• *Prescription only medicine* • *Treatment with dabrafenib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products*	*None*

The Risk Minimisation Plan is endorsed.

The CHMP endorsed this advice without changes.

2.9. User consultation

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

3. Benefit-Risk Balance

Benefits

Beneficial effects

One pivotal trial (BREAK-3) was submitted in support of the efficacy of dabrafenib therapy in patients with unresectable or metastatic melanoma with a BRAF V600 mutation. The superiority of darbafenib over DTIC was convincingly demonstrated in terms of the primary endpoint progression free survival. Median PFS was 6.9 months in the dabrafenib group and 2.7 months in the DTIC group (HR 0.37).This effect was further substantiated by results in the secondary efficacy endpoints: overall response rate was significantly greater in dabrafenib treated patients compared to the DTIC group (59% vs. 24%) and in the updated OS analysis a trend in favour of dabrafenib is shown (HR=0.76, 95% CI: 0.48, 1.21).

The two phase II studies provided additional support concerning the anti-tumour effect of dabrafenib in subjects with BRAF V600 mutation: In BREAK-2, confirmed objective response was 59% and 13% for subjects with BRAF V600E and BRAF V600K mutation, respectively. In BREAK-MB, the overall response rate in patients with BRAF V600E metastatic melanoma was 38 % and 31% for locally non-pretreated and pretreated patients, respectively. In patients with BRAF V600K mutation positive metastatic melanoma the response rate was 28 % for pre-treated patients.

With respect to assays used for the detection of V600 mutations during drug development, sufficient data have been submitted to support the credibility of assay results, this also in relation to the CE marked THxID BRAF assay.

Treatment effect on PFS was consistently favourable across all subgroups (number of metastatic disease sites, ECOG PS, visceral disease; baseline lactate dehydrogenase; sex and disease stage).

The efficacy results in terms of PFS and ORR are similar to the authorized vemurafenib (BRAF V600 inhibitor) based on indirect comparisons.

Uncertainty in the knowledge about the beneficial effects

Patients with melanoma driven by BRAF mutations other than V600E were excluded from the confirmatory trial and with respect to patients with the 600K mutation in single arm studies the activity appears lower than in V600E tumours. This has been reflected adequately in section 5.1 of the SmPC.

Risks

Unfavourable effects

The most common events were hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, papilloma, alopecia, rash and vomiting.

About 10% of all patients developed cutaneous squamous epithelial cell carcinoma, keratoacanthoma and Bowen´s disease which both are low grade squamous epithelial carcinomas. There could also a risk for other solid and haematologic malignancies; two cases with verified RAS mutations are reported. The most frequent SAEs in the dabrafenib group were cutaneous SCC (8%) and pyrexia (5%). A total of 5 subjects in the integrated dabrafenib safety population experienced a Grade 5 SAE, none of which were attributed to study treatment. There are uncommon adverse events that are of concern such as uveitis/ iritis, pancreatitis, panniculitis and renal failure. The majority of these events also seem to be class related.

Dabrafenib is a strong inducer of drug-metabolising enzymes. It may therefore decrease the plasma concentrations and thereby potentially the efficacy of many medicines.

Uncertainty in the knowledge about the unfavourable effects

Long term data is missing, with regards to other squamous epithelial and other malignancies apart from cutaneous SCC. Since a mechanism of paradoxical RAS activation is identified and there are clinical reports of both solid tumours and haematologic malignancies further information and follow-up on long-term treatment is needed in general, but for malignancies in particular. This additional information to be provided is included in the RMP and appropriate wording has been implemented in section 4.4 of the SmPC. Furthermore there are two on-going studies to address this safety issue and cumulative semi-annual reports for non-cutaneous malignancies will be provided by the applicant.

Benefit-risk balance

Importance of favourable and unfavourable effects

The pivotal study has shown a clinically relevant effect of dabrafenib for PFS and thus, a clinical benefit has been convincingly demonstrated. The CHMP considers that the clinical benefit is relevant to the proposed indication.

The adverse events reported were adequately described and were considered acceptable. Cutaneous squamous epithelial malignancies are clinically manageable, other events of concern although relatively uncommon like pancreatitis and renal failure could be managed with relevant pharmacovigilance measures to limit the clinical effects. The possible increase of other malignancies will be followed in clinical studies and safety updates. The overall toxicity profile of dabrafenib seems acceptable and SAEs known to be related to dabrafenib treatment are mostly manageable.

Benefit-risk balance

Overall, the efficacy of dabrafenib has been demonstrated. The adverse event profile of dabrafenib seems acceptable and generally manageable. The benefit-risk balance for dabrafenib for the treatment of unresectable or metastatic melanoma with a BRAF V600 mutation is considered positive. The favourable effects outweigh the negative effects of Tafinlar.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Tafinlar in the treatment of unresectable or metastatic melanoma with a BRAF V600 mutation is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

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

- **Additional risk minimisation measures**

Not applicable

- **Obligation to complete post-authorisation measures**

Not applicable.

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

Not applicable.

New Active Substance Status

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