15 December 2011
EMA/200986/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zelboraf

vemurafenib

Procedure No.: EMEA/H/C/002409

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Product information

Name of the medicinal product:	Zelboraf
Applicant:	Roche Registration Ltd. 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom
Active substance:	vemurafenib
International Non-proprietary Name/Common Name:	vemurafenib
Pharmaco-therapeutic group (ATC Code):	Protein kinase inhibitors (L01XE15)
Therapeutic indication:	Vemurafenib is indicated in monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma (see section 5.1).
Pharmaceutical form:	Film-coated tablet
Strength:	240 mg
Route of administration:	Oral use
Packaging:	blister (alu/alu)
Package size:	56 tablets

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List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
bid	Twice daily
BLQ	Below the limit of quantisation
BORR	Best overall response rate
BRAF	Serine/threonine-protein kinase B-Raf
BRAFV600	Codon 600 position of BRAF gene, site of oncogenic mutations
BRAFwt	Wild-type BRAF gene
CI	Confidence interval
CL/F	Apparent clearance in blood after oral administration, calculated as Dose/ AUC0-∞ after a single dose or Dose/AUC0-τ at steady state after repeated administration
C_{min}	Pre-dose trough blood concentration in a dosing interval
CR	Complete response
CRC	Colorectal Cancer
CT	Computed tomography
cuSCC	Cutaneous squamous cell carcinoma
CV	Constant volume
CYP	Cytochrome P450
DLT	Dose-limiting toxicities
DSMB	Data Safety Monitoring Board
DTIC	Dacarbazine ([3,3-Dimethyl-1-triazenyl]imidazole-4-carboxamide)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EU	European Union
GLP	Good laboratory practice
IC50	Concentration that induced half-maxiaml inhibition of cell viability
INN	International Non-proprietary Name
IP	Intraperitoneal
ITT	Intent-to-treat
KA	Keratoacanthoma
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
M1a	Stage of melanoma that is defined by distant skin, subcutaneous, or lymph node metastases and normal LDH
M1b	Stage of melanoma that is defined by lung metastases and normal LDH
M1c	Stage of melanoma that is defined by all other visceral metastases, normal LDH, any distant metastases, elevated LDH
MBP	Microprecipitated Bulk Powder
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute CTCAE Common terminology criteria for adverse events
OS	Overall survival
PBT	Persistent, Bioaccumulative and Toxic
Ph Eur	European Pharmacopeia
PD	Pharmacodynamic
PK	Pharmacokinetic
PFS	Progression-free survival
p.o.	*per os*
PP	Per protocol
PR	Partial response
QTcP	QT analysis corrected population
RECIST	Response Evaluation Criteria In Solid Tumours

SAP	Statistical analysis plan
SAE	Serious adverse events
SCC	Squamous cell carcinoma
SE	Standard error
ULN	Upper limit of normal
US	United States

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration Ltd. submitted on 4 May 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zelboraf, 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 28 September 2010.

The applicant applied for the following indication: Vemurafenib is indicated for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma (see section 5.1).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The 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/345/2010 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant requested the active substance vemurafenib contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 24 September 2009, 22 April 2010 and 18 November 2010. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: US.

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

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

Rapporteur: **Tomas Salmonson** Co-Rapporteur: **Barbara van Zwieten-Boot**

- The application was received by the EMA on 4 May 2011.
- Accelerated Assessment procedure was agreed-upon by CHMP on 14 April 2011.
- The procedure started on 25 May 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 August 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 August 2011. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 19-22 September 2011, 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 22 September 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 October 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 November 2011.
- During the CHMP meeting on 14-17 November 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 24 November 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 9 December 2011.
- During the meeting on 12-15 December 2011, 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 Zelboraf on 15 December 2011.

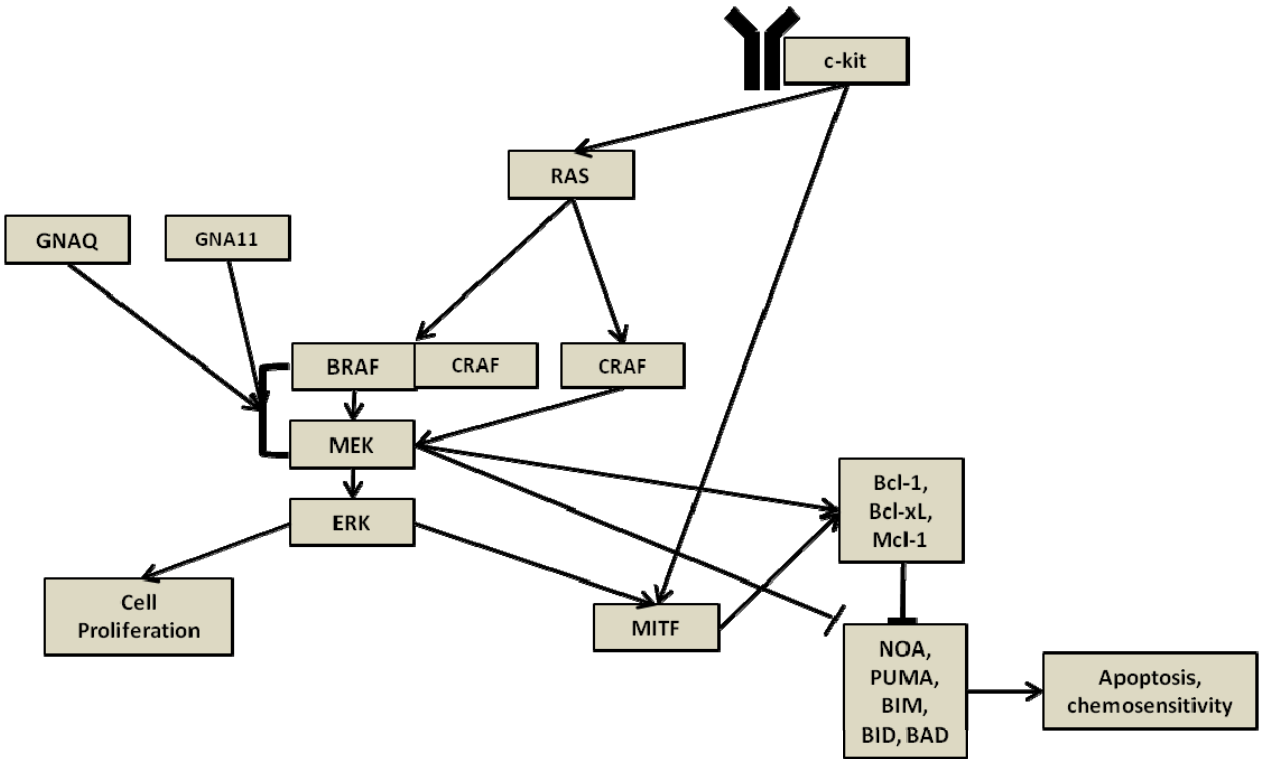
2. Scientific discussion

2.1. Introduction

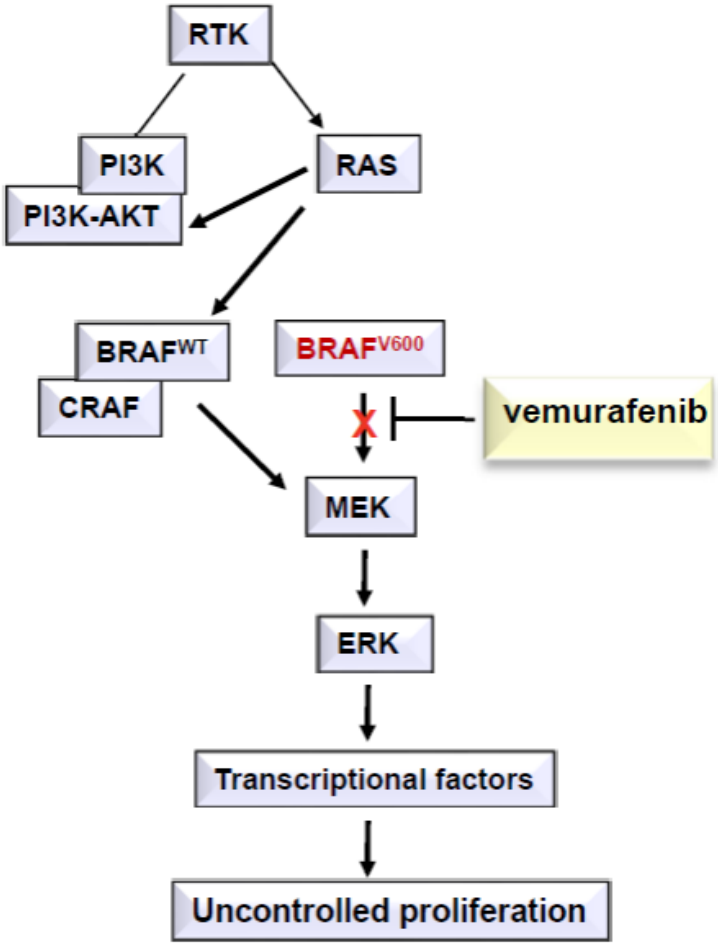
Melanoma is the sixth and seventh most common malignancy in men and women, respectively. The median age at diagnosis is 59 years. In Europe, approximately 26,100 males and 33,300 females are diagnosed annually with melanoma, and approximately 8,300 males and 7,600 females die from the disease every year. The outcome of melanoma depends on the stage at presentation. When detected early and treated with adequate surgery, the prognosis of localized disease (thin lesions <1.0 mm without adverse prognostic features) is excellent with greater than 90% survival. However, for patients with unresectable or metastatic disease, the prognosis remains poor: the 1 year survival rate is 25.5% and 5-year survival rate is lower than 15%.

In EU Countries, dacarbazine has been used as standard first line treatment of patients with metastatic melanoma[1]. Clinical trials with dacarbazine have shown low response rates ranging from 11% -25%, low rate of complete responses and of short duration (3 to 6 months). The median survival time ranged from 4.5 to 6 months[2, 3,4]. Ipilimumab, a human monoclonal antibody against CTLA-4, was recently approved in the EU for melanoma patients who have received prior therapy. In recent times, the serine-threonine kinase BRAF, was discovered mutated in many cancers[5]. BRAF mutations have been found in approximately 50% of melanoma, 30-70% of thyroid carcinomas, 30% of ovarian carcinoma and 10% of colorectal carcinoma. Oncogenic mutations in BRAF result in constitutive activation of the RAF-MEK-ERK pathway which in turn stimulates cell growth, proliferation and cell survival in the absence of typical growth factors[6]. Oncogenic BRAF phosphorylates and activates MEK which in turn phosphorylates ERK (pERK), and pERK translocates into the nucleus where it activates transcriptional factors that are responsible for stimulating cell proliferation and cell survival (Figure 1).

Figure 1 **Vemurafenib inhibits activated BRAF kinase and as such it suppresses the RAF-MEK-ERK kinase signalling pathway ultimately leading to proliferation inhibition**



[1] Serrone L, Zeuli M, Sega FM, et al: Dacarbazine- based chemotherapy for metastatic melanoma: Thirty year experience overview. J Exp Clin Cancer Res 19:21-34, 2000
[2] Luce JK, Thurman WG, Isaacs BL, et al: Clinical trials with the antitumor agent 5-(3,3– dimethy-1-triazeno)imidazole-4-carboxamide. Cancer Chemother Rep 54:119-124, 1970
[3] Hill GJ, Moss SE, Golomb FM, et al: DTIC and combination therapy for melanoma. Cancer 47:2556-2562, 1981
[4] Falkson G, Van der Merwe AM, Falkson HC: Clinical experience with 5-(3,3–bis(2-chloroethyl)- 1-triazeno)-imidazole-4-carboxamide (NSC 82196) in the treatment of metastatic malignant melanoma. Cancer Chemother Rep 56:671-677, 1972
[5] Davies H, et al. Mutations of the BARF gene in human cancer. Nature; 417:949-954, 2002
[6] Garnett MJ and Marais R. Guilty as charged: B-RAF is a human oncogene. Cancer Cell 6:313-319, 2004



The most frequently observed BRAF mutation in melanoma was shown to be V600E (74-90%). followed by V600K (15-25% of V600 mutations), V600R and V600D. Other more rare mutations (i.e. V600A, V600M and V600G) have also been described. Vemurafenib is a low molecular weight, orally available, inhibitor of the activated form of oncogenic BRAF. It suppresses downstream signalling through the mitogen-activated protein kinase (MAPK) pathway. Since vemurafenib targets inhibition of oncogenic BRAF V600E, only patients whose tumours tested positive for BRAFV600E mutations by a companion diagnostic test (i.e., the cobas 4800 BRAF V600E Mutation Test) were considered eligible for enrolment into vemurafenib clinical trials.

The Applicant was seeking an accelerated approval for vemurafenib (Zelboraf), for the treatment of melanoma patients harbouring BRAF V600 mutations, which represents a significant subgroup of the population treated in clinical practice. The CHMP agreed that at the time of submission, there was an unmet medical need with regards to medicinal products that could prolong overall survival in melanoma patients and that the product could change clinical practice in the EU and thus was of major interest from the view of public health and therapeutic innovation. Thus, The CHMP granted accelerated assessment for Zelboraf.

The recommended dose of vemurafenib is 960 mg (4 tablets of 240 mg) twice daily (equivalent to a total daily dose of 1,920 mg). The first dose is to be taken in the morning and the second dose is to be taken approximately 12 hours later in the evening. Vemurafenib tablets are to be swallowed whole with water. Vemurafenib tablets should not be chewed or crushed.

2.2. Quality aspects

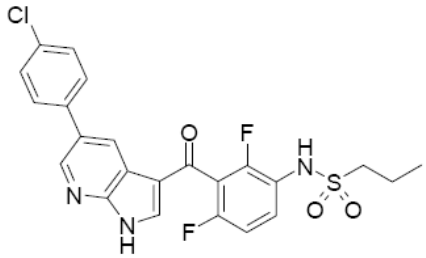
2.2.1. Introduction

Zelboraf is presented as film-coated tablets containing 240 mg of amorphous vemurafenib as active substance packaged in standard aluminium/aluminium blisters. The excipients used in the tablet core are colloidal anhydrous silica, croscarmellose sodium, hydroxypropylcellulose, and magnesium stearate. They comply with their respective compendial monographs of the Ph Eur. The use of the excipients in the formulation has been justified and their functions explained.

2.2.2. Active Substance

The drug substance, vemurafenib, is a new chemical entity. It is manufactured as the amorphous form and processed with hydroxypropyl methylcellulose acetate succinate (HPMC-AS) in a ratio of 3:7 (w:w). This is performed in order to keep the active moiety as the desired amorphous modification so as to achieve enhanced dissolution of the substance.

The chemical name of vemurafenib is Propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro- phenyl}-amide.



The chemical structure of vemurafenib has been verified by elemental analysis (C, H, N, S, Cl, S, F, O), UV spectroscopy, IR spectroscopy, 1H-NMR, 13C-NMR, mass spectroscopy and X-ray powder diffraction spectroscopy.

Vemurafenib can exist as several polymorphs and solvates. The crystalline Form II is thermodynamically the most stable.

Crystalline vemurafenib (Form II) is a white to almost white non-hygroscopic powder with a melting point of about 271°C. Its solubility in water is very low (<0.0001 mg/ml) and it is not appreciably soluble in many common organic solvents either.

When processed with HPMC-AS, vemurafenib becomes an amorphous white to almost white powder which is slightly hygroscopic. The product with (HPMC-AS) is non-crystalline.

Manufacture

The synthesis process of the active substance vemurafenib (HPMC-AS) involves six different steps, the first four of which comprise the formation of the active moiety vemurafenib, and then the other two complete the formation of vemurafenib with HPMC-AS. The manufacturing process has been suitably described in flow charts and a narrative description. In the synthesis process, five intermediates are isolated.

The starting materials are controlled to justified and acceptable specifications. Descriptions of the synthesis routes of the starting materials have been enclosed. The analytical methods used in the control of the starting materials have been validated as applicable.

The specified impurities are common in the active moiety, vemurafenib, and in vemurafenib/HPMC-AS formulation, and they are controlled at the same level. The analytical methods used in the control of the intermediates have been enclosed and they have been satisfactorily validated.

Specification

The specifications of the active substance contains tests with suitable limits for appearance (visual), Identification (IR and HPLC), water (Ph Eur), microbiological purity (Ph Eur), residual solvents (GC), assay (HPLC), heavy metals (dispersive X-ray fluorescence spectrometry), particle size (laser diffraction), sulphated ash (Ph Eur) and impurities (HPLC). The Applicant has provided a toxicological justification for the proposed levels of impurities.

To verify the non-crystalline modification of the drug substance, X-ray powder diffraction analysis is performed. The diffraction pattern of the sample is compared with the patterns of the amorphous vemurafenib/HPMC-AS and crystalline vemurafenib Form II reference materials (the vemurafenib Form II is mixed with HPMC-AS in a ratio of 30:70).

Stability

Primary stability studies according to ICH guidelines have been initiated on pilot and commercial scale batches of the drug substance stored in the commercial package. Six months of accelerated data are available for all batches and up to 24 months of data have been reported for the long term condition. The parameters tested included assay, purity, related substances, appearance, colour, water content, HPLC identity, particle size distribution and amorphous modification. All results reported are within proposed specifications.

The amorphous modification remains stable in all cases both at the accelerated and the long term condition. No change in appearance/colour or in particle size distribution is observed over time. The assay values remain stable and there is no decrease in purity with time at either condition.

The drug substance has also been subjected to forced degradation both in the solid state and in solution/suspension. Light exposure brings about an increase in the hydroxymethyl impurity RO6808065 and the same impurity increased after treatment at forced degradation for 14 days. In solution/suspension, treatment with dilute hydrogen peroxide for 14 days is stated to induce the formation of the N-oxide RO6800721. This impurity has, however, not been found under ICH conditions.

The proposed re-test period with the storage conditions "Do not store above 30°C. Store in closed containers protected from light and humidity" is considered acceptable.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The pharmaceutical development has been adequately described. Vemurafenib is a compound with low permeability and very low solubility and this has been taken into account in the development. The difficulties with crystalline vemurafenib as regards solubility and bioavailability have been acceptably

discussed, and the development towards a film-coated tablet comprising the amorphous substance in co-precipitation with HPMC-AS, has been well described and justified.

To ensure good processing properties and satisfactory dissolution the drug substance is milled and controlled with respect to particle size distribution. The water content of the drug substance is also considered critical as well as the amorphous modification. The manufacturing process has been developed to comprise a dry granulation and thereby avoiding water in the process. By this, formation of crystalline Form II is avoided during manufacturing. The dry granulation is performed by roller compaction and this operation was optimized.

The first clinical trial was conducted on a capsule formulation with 100 mg and 300 mg micronized crystalline Form I of vemurafenib. Form I of vemurafenib gradually transformed to Form II and the bioavailability observed was low. The need for another formulation was acknowledged and the amorphous form was developed. The amorphous form was found to be more soluble and bioavailable than the crystalline form and it was subsequently used in all clinical studies. The same 240 mg film-coated tablet as developed for the clinical studies will also be used for the commercial tablet.

The manufacturing process development has resulted in a robust manufacturing process for the finished product. Critical steps and attributes have been adequately addressed.

Adventitious agents

Not applicable.

Manufacture of the product

The film-coated tablets are manufactured by a standard process comprising blending, screening, dry granulation, tablet compression and film-coating. Critical steps have been identified and properly evaluated at the commercial scale.

The reproducibility of the process has been suitably demonstrated. Formal validation will be performed post-approval on the first three consecutive commercial batches. An acceptable validation plan for this activity has been provided.

Product specification

The drug product is controlled by testing attributes relevant for this dosage form. The film-coated tablets are tested for appearance, identification by HPLC retention time and UV spectrum, water content (KF), dissolution, control of amorphous form (X-ray powder diffraction spectrometry), uniformity of dosage units(mass variation/ Ph Eur), assay (HPLC) and, degradation products (HPLC). The tablets comply with Ph Eur criteria for microbiological quality.

The analytical methods used in the control of the drug product have been satisfactorily validated according to ICH guidelines where necessary. Batch analysis data in compliance with the specifications have been provided for six pilot and three production scale batches.

Stability of the product

Stability studies have been initiated according to ICH guidelines on both pilot and production scale batches of the finished product packaged in its commercial Al/Al blister package. Six months of accelerated data are reported for the batches and up to 24 months of long term data are at hand for the pilot scale batches and nine months from the production scale batches. The batches are monitored for description, assay, degradation products, water content, modification, and dissolution. No

significant changes or trends in any of the parameters have been seen so far in the primary stability studies and all data are within proposed specifications. No change in modification has been observed in any instance and no change in dissolution profiles is seen. No increase in water content is reported in any batch at any condition and the assay remains unchanged throughout. There is no observed increase in degradation products over time.

Stressed testing (photo-stability, open storage at high temperature and high and low moisture) has also been conducted on batches of the finished product. Tablet powder has also been subjected to aqueous acid, alkaline and oxidative conditions. The results of the stressed studies show that the tablets are not sensitive to light. An environment of high moisture and temperature or high moisture alone brought about changes in the amorphous vemurafenib modification which gradually transformed to crystalline Form II at such conditions.

The film-coated tablets have been proven stable in the proposed Al/Al blister package after 6 months at the accelerated condition and up to 24 months after long term ICH storage. So far no crystalline Form II of the drug substance has been detected.

Based upon the stability data provided, the proposed shelf-life and storage conditions are considered acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality of Zelboraf is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements.

Since the drug substance active moiety, vemurafenib, is practically insoluble in aqueous media (especially in crystalline form) and it has very low bioavailability. To improve solubility and bioavailability the substance, in its amorphous form, has been processed with hydroxypropylmethylcellulose acetate succinate. This process renders the vemurafenib amorphous. The amorphous form of vemurafenib is confirmed at release and during stability studies by X-ray diffraction spectrometry. Also, the water content is controlled to ensure that the amorphous form will be maintained in the substance.

The development of the 240 mg vemurafenib film-coated tablets has been well described and has resulted in a finished product which consistently and reproducibly complies with its proposed specifications. The excipients are commonly used in these types of formulations and comply with Ph. Eur. requirements. The packaging material is commonly used and well documented. The manufacturing process of the finished product has been adequately described. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the 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. There are no unresolved quality issues.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Non-clinical pharmacology studies submitted to evaluate the effect of vemurafenib on cancer cells included *in vitro* biochemical, anti-proliferative, anti-tumour, and mechanism of action studies.

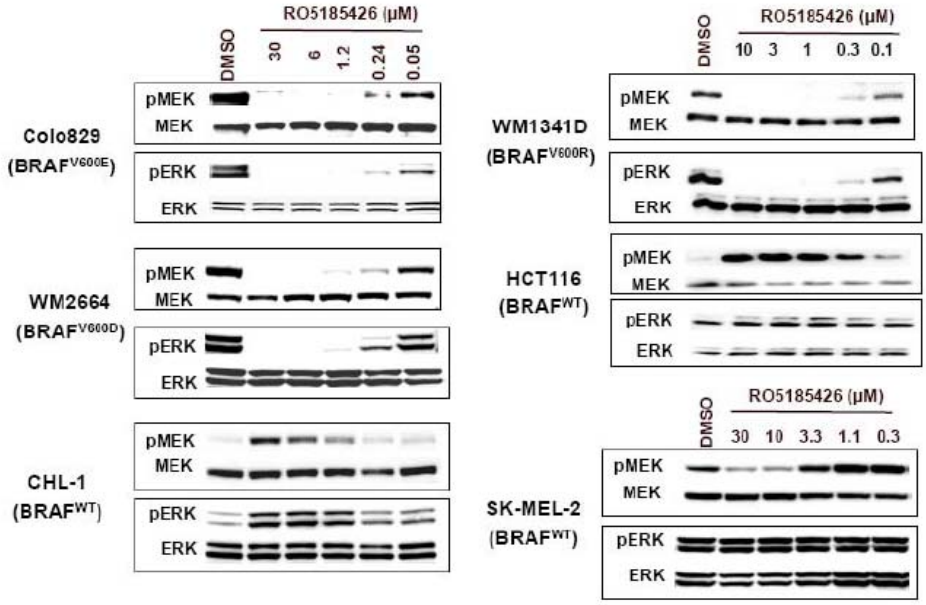
2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro mechanistic studies

The effect of vemurafenib on RAF-MEK-ERK pathway inhibition was investigated in a panel of cancer cell lines, including melanoma cell lines expressing BRAFV600E, BRAFV600D, BRAFV600R, or BRAFWT. MEK and ERK phosphorylation (pMEK and pERK respectively) immunoassays were conducted to measure the levels of pMEK and pERK in various cancer cells treated with vemurafenib compared to vehicle control (Figure 2).

Figure 2 Cellular Effect of vemurafenib on downstream targets MEK and ERK phosphorylation in cancer cells expressing BRAFV600E, BRAFV600D, BRAFV600R mutant kinase and BRAFWT kinase



In cells expressing mutated BRAF (Colo829,WM2664 and WM1341D), vemurafenib inhibited both pERK and pMEK in a dose dependent manner. However, cells expressing BRAF WT vemurafenib induced rather than inhibited ERK or MEK phosphorylation in the cells expressing BRAFWT, such as HCT116, CHL-1 and SK-MEL-2 cells.

Cellular proliferation was assessed in a panel of cancer cell lines, including melanoma cell lines expressing BRAFV600E, BRAFV600D, BRAFV600R, BRAFV600K or cells that express BRAFWT and harbour RAS mutations following vemurafenib treatment. Results are shown in Table 1 and 2.

Table 1 IC50 values against a panel of cancer cell lines

Tumour	**Melanoma**			**Colorectal**		**NSCLC**	
Oncogen	**BRAF (V600E)**			**BRAF (V600E)**	**KRAS (G12V)**	**NRAS (Q61K)**	**KRAS (Q61H)**
Cell line	**A375**	**WM2664***	**COLO829**	**COLO20**	**SW620**	**H1299**	**H460**
IC_{50}	0.55	0.42	0.081	0.042	5.6	13	8.9

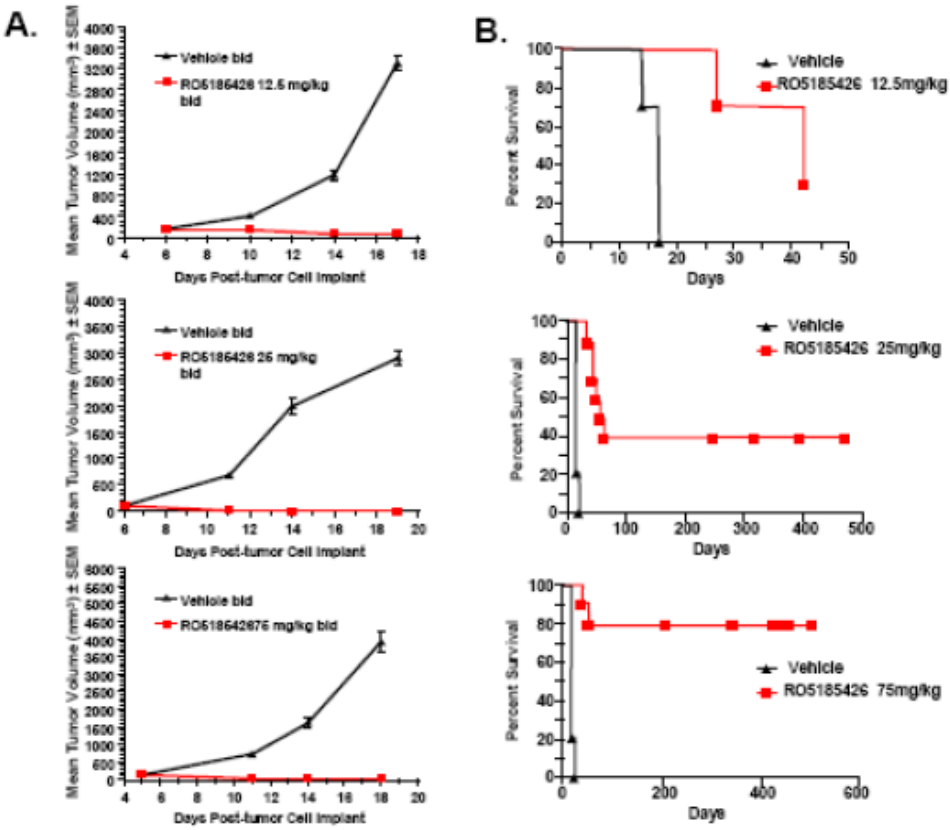
Table 2 IC50 values against a panel of cancer cell lines

Melanoma Cell line	**BRAF status**	**RAS status**	**Proliferation IC50 (uM)**
MALME-3M	V600E	WT	0.016
Colo829	V600E	WT	0.030
Colo38	V600E	WT	0.042
A375	V600E	WT	0.057
WM1341D	V600R	WT	0.063
SK-MEL28	V600E	WT	0.089
WM2664	V600D	WT	0.150
SK-MEL5	V600E	WT	0.164
HT144	V600E	WT	0.165
LOX	V600E	WT	0.223
WM239A	V600D	WT	0.281
WM3152	V600K	WT	0.925
A2058	V600E	WT	1.131
WM1789	K601E	WT	2.047
HMVII	G469V	NRASQ61K	10.43
CHL-1	WT	WT	12.06
SK-MEL-2	WT	NRASQ61R	14.32

In vivo mechanistic studies

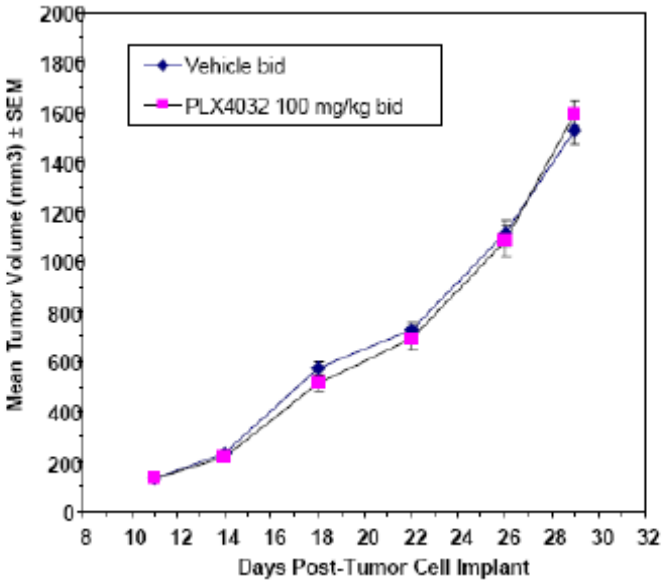
The *in vivo* activity of vemurafenib was assessed in a mouse xenograft study in which BRAFV600E–expressing LOX melanoma cells were implanted into the flank of female athymic NU-Foxn1nu nu/nu mice. Tumours were allowed to grow to a size of 100 mg, and daily administration of vemurafenib or vehicle control was initiated on Day 5 or 6 after implant and continued for 13 days. Results are shown in Figure 3.

Figure 3 *In vivo* mechanistic studies in the LOX melanoma xenograft model. (A) vemurafenib inhibition of tumour growth and tumour regression in three doses, (B) Survival relative to vehicle



To assess the *in vivo* selectivity of vemurafenib against BRAFWT compared to mutant BRAFV600E, vemurafenib was administrated to female nude mice bearing HCT116 xenograft tumours which expressed BRAFWT. Treatment with vemurafenib began after HCT116 cell implantation and animals were dosed twice daily for 18 days. No inhibition of tumour growth observed with the administration of 100 mg/kg twice a day (bid) of vemurafenib in the HCT116 xenograft model which expressed only BRAFWT.

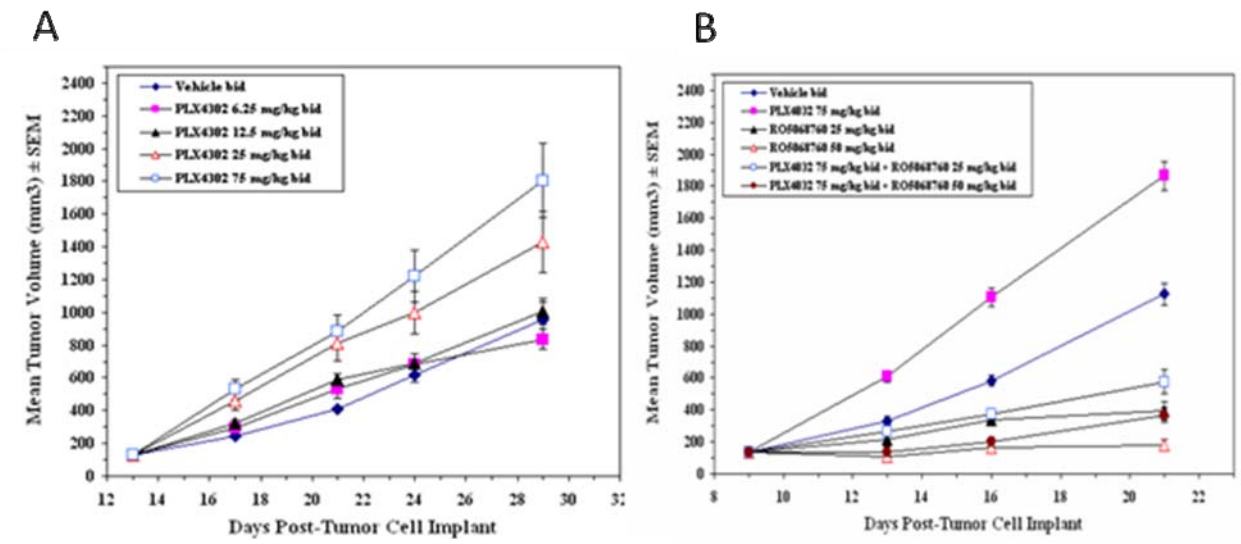
Figure 4 Treatment of mice expressing BRAFWT xenograph tumours



Secondary pharmacodynamic studies

Cutaneous squamous cell carcinoma (cuSCC) has been reported in patients with metastatic melanoma and CRC treated with vemurafenib. Clinical findings indicate that cuSCC may be related to treatment with vemurafenib. In order to understand the potential mechanism by which vemurafenib treatment contributes to development of cuSCC, vemurafenib was tested *in vivo* in the A431 cuSCC xenograft model. There was dose-dependent tumour growth stimulation of the xenograft tumours at doses higher than 25 mg/kg bid (Figure 5A). The optimal dose of 75 mg/kg bid of vemurafenib caused a 103% induction of growth compared to the control (p=0.002). Immunohistochemistry showed staining of pERK only in the tumour samples treated with vemurafenib (75 mg/kg) as compared to the vehicle treated control group. Combination studies of vemurafenib and a MEK inhibitor, RO5068760, were performed to confirm inhibition of pERK. Results are shown in Figure 5B.

Figure 5 **(A) vemurafenib treatment contributes to development of cuSCC, vemurafenib was tested *in vivo* in the A431 cuSCC xenograft model (PLX4302 = vemurafenib). (B) Combination studies of vemurafenib and the MEK inhibitor, RO5068760**



Safety pharmacology programme

Cardiovascular system

The applicant performed a number of *in vitro* (Study NOVA05-2468-RR1041083; Study WIL578008-RR1040807; WIL578011-RR1080810) and *in vivo* (Study WIL578013-RR1040811; Studies 10164-RR1025759 and 11260-RR1032862) studies to investigate the effect of vemurafenib on the cardiovascular system.

Lower systolic, diastolic, and mean blood pressures were recorded for all treatment groups from 11 to 12 hours post-dosing through termination of recordings. The NOAEL for vemurafenib was 1000 mg/kg (estimated Cmax = 42 µM, about half of the Cmax (~90 µM) observed in patients dosed at 960 mg bid). In the repeat-dose GLP toxicity studies in dogs, ECGs were evaluated for heart rate and

waveform intervals (PR, QRS, RR, QT, and QTc), all of which were qualitatively and quantitatively within normal limits (up to steady state Cmax = 91 µM, which is comparable to the Cmax (~90 µM) observed in patients dosed at 960 mg bid).

Central Nervous System

The applicant performed an *in vivo* study (Study WIL-30031-RR1026179) to investigate the effect of vemurafenib on the central nervous system. vemurafenib was administered as a single oral dose to male Sprague Dawley rats at doses of 0, 30, 100, or 1000 mg/kg (corn oil formulation). Animals were observed twice daily for mortality and moribundity. The positive control, chlorpromazine, produced the expected cascade of CNS depression. The NOAEL of vemurafenib was 1000 mg/kg with an estimated Cmax of 160 µM.

Respiratory System

The applicant performed an *in vivo* study (Study WIL-30030-RR1026178) to investigate the effect of vemurafenib on the respiratory system. Vemurafenib was administered as a single oral dose to male Sprague Dawley rats at doses of 0, 30, 100, or 1000 mg/kg (corn oil formulation). The NOAEL of vemurafenib was found to be 1000 mg/kg with an estimated Cmax of 160 µM.

Pharmacodynamic drug interactions

The applicant did not submit non-clinical pharmacodynamic drug interaction studies.

2.3.3. Pharmacokinetics

The applicant presented PK data from over 40 studies, many of which related to the optimization of the vemurafenib formulation. Vemurafenib was analyzed in plasma from animals by several methods at different stages of development. In all methods, plasma was analyzed by protein precipitation followed by HPLC chromatography and analyte detection using positive ion electrospray tandem mass spectrometry (LC/MS/MS).

An overview of the most important pharmacokinetic parameters for comparison of rat, dog, rabbit and human is given in Table 3.

Table 3 Overview of the most important pharmacokinetic parameters for interspecies comparison between rat, dog and human

Species	Route	Formulation	Feeding condition	Dose (mg/kg)	AUC (µg*h/mL) (%CV)	$T_{1/2}$ (h)	V_{ss} (L/kg)	F (%)	Study
rat	PO^	MBP	fed	30	70.5 (111) 172 (15)	~3	0.25	18 43	1041429 1041430 1040851
dog	PO	MBP	fed	24.5	62.1 (42)	~2	0.69	40	1041444 1040853
rabbit	PO^	suspension of API, HPMC-AS, Aerosil 200	fed	50	158 (63)	~15	-	-	1041434
human	PO	MBP film-coated tablet	fasted	27.4	130.6 (38)	57	1.3*	-	NP25163 SPC

^ Intubation

API = active pharmaceutical ingredient

*Vss/F

Absorption

Single dose studies to determine pharmacokinetics were conducted in mouse, rat, rabbit, dog and monkey. In all pre-clinical species, half-lifes were between 2 and 5 hours and the volume of distribution between 0.25 (12% CV) and 0.69 (39% CV) L/kg. Only after intraperitoneal (IP) administration in mice, the half-life was much longer (20.6 h). Compared with other species, rabbits showed higher plasma exposure levels with a longer mean terminal half-life between 12 and 18 hours.

Two oral repeated dose studies have been conducted in both male and female dogs with twice-daily doses as MBP formulation of 50, 150 and 450 mg/kg for 37 days and with twice-daily doses of 75 and 150 mg/kg for 92 days. In dogs, the bioavailability was 10% after oral administration of vemurafenib in Phase I formulation and ~40% in MBP formulations. No gender differences were observed in systemic exposure. AUC and C_{max} were less than dose-proportional in both male and female dogs suggesting saturation of absorption.

Distribution

Plasma protein binding data was independent of the compound concentration (250-50000 ng/mL) for all species studied. The average percent plasma protein binding was 99.81± 0.07, 99.85 ± 0.06, 99.79 ± 0.09, 99.82 ± 0.10 and 99.86 ± 0.06 for mouse, rat, dog, monkey and human, respectively.

Percent binding of 14C-vemurafenib to human serum albumin was 99.80 ± 0.13. The overall percent binding of 14C-vemurafenib to alpha-1 acid glycoprotein was 99.18 ± 0.23.

The blood to plasma ratio for 14C-vemurafenib was 0.63 ± 0.03, 0.60 ± 0.04, 0.68 ± 0.04, 0.85 ± 0.05 and 0.58 ± 0.03 for mouse, rat, dog, monkey and human, respectively. The overall percent of 14C-vemurafenib associated with red blood cells was 15.42 ± 4.48, 15.23 ± 5.01, 20.04 ± 3.93, 39.88 ± 3.13, and 11.40 ± 3.75 for mouse, rat, dog, monkey and human, respectively.

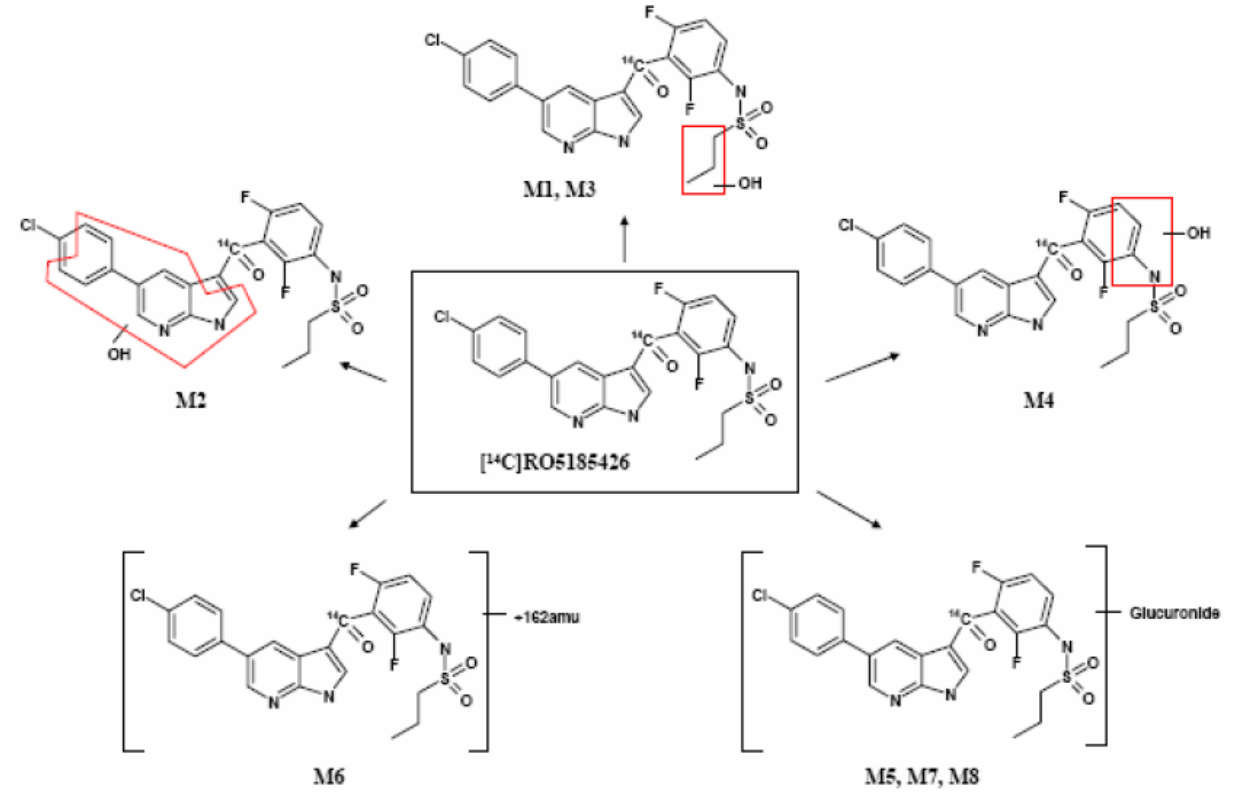
Concentrations of radioactivity in tissues were relatively similar to blood concentrations at all time points with concentrations present in almost all tissues at the earliest sampled time points (0.5 to 12 h post-dose), except for liver, kidney, adrenal cortex, lachrymal glands, lung, and alimentary canal tissues, which were generally higher than that in blood. High concentrations were observed in gastrointestinal contents (Cmax 92.694 to 6950.564 µg equiv/g) and bile (Cmax 91.437 µg equiv/g at 4 h). Concentrations in tissues generally decreased over the course of the study and most tissues (39 out of 43) were below the limit of quantisation (BLQ) by 24 hours post dose, except for the small intestine, skin, pancreas, liver, and stomach. Selective distribution and retention in melanin-containing tissues of the eye (uveal tract) or skin was not detected. Concentrations in the brain and spinal cord were BQL throughout the duration of the study. Elimination appeared to be complete at 96 h post-dose.

Metabolism

In vitro metabolism was analyzed for rat, mouse, dog, cynomolgus and human. The metabolism of vemurafenib was investigated both *in vitro* using microsomes and hepatocytes of various species and *in vivo* in rat, dog and human. *In vitro* analysis of vemurafenib metabolism in liver hepatocytes at the concentration of 10 uM, humans, dogs, and cynomolgus monkeys did not metabolize vemurafenib extensively (unchanged vemurafenib ≥ 89%).

Metabolic schematics are presented in Figure 6.

Figure 6 Biotransformation pattern in humans



The results from *in vitro* studies indicate that CYP3A4 was the major enzyme responsible in the metabolism of vemurafenib. The formation of mono-hydroxyl metabolites were inhibited for ~82% using the CYP inhibitor ketoconazole. No significant inhibition in the metabolism was observed in human liver microsomes in the presence of quinidine (CYP2D6 inhibitor), sulfaphenazole (CYP2C9 inhibitor), tranylcypromine (CYP2A6 inhibitor) and (-)-N-3-benzyl-phenobarbital (CYP2C19 inhibitor). In addition, CYP3A4 was responsible for the formation of the mono-hydroxylation metabolites.

Metabolic profiles were evaluated *in vivo* in rat (plasma and excreta), dog (plasma) and humans (plasma and excreta) and are shown in Table 4.

Table 4 Metabolism of vemurafenib in rat, dog and humans

	rat (5 mg/kg) (IV dosing)			**rat (100 mg/kg) (oral dosing)**			**dog (600 mg/kg) (D19 of oral dosing)**			**human (27.4 mg/kg) (D15 of oral dosing)**		
	plasma (0-2 h)	**urine (0-24 h)**	**faeces (8-24 h)**	**plasma (0-2 h)**	**urine (0-24 h)**	**faeces (8-24 h)**	**plasma (9-11 h)**	**urine**	**faeces**	**plasma (36-48 h)**	**urine (0-96 h)**	**faeces (48-96 h)**
	percentage of dose			**percentage of dose**			**percentage of dose**			**percentage of radioactivity (% of dose)**		
vemurafenib	15.5	0.3	11	43	ND	72	98	NM	NM	96	32 (1.0)	56 (17)
M1	0.4	1.3	49	3.0	ND	11	1.3-1.5	NM	NM	ND	ND	ND
M3	0.5	0.13	8.3	1.8	ND	1.9	0.7-0.8	NM	NM	4	7.4 (0.05)	14 (3.3)
M4	ND	ND	2.9	ND	ND	1.1	ND	NM	NM	ND	ND	ND

M6	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	30 (0.24)	19 (5.0)
M8	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	12 (2.9)
M9	ND	ND	4.6	ND	ND	0.6	ND	NM	NM	ND	ND	ND
M10	0.1	ND	2.5	0.7	ND	0.4	ND	NM	NM	ND	ND	ND
M11ab	ND	ND	ND	ND	ND	ND	ND	NM	NM	ND	ND	ND
M12	0.03	ND	ND	ND	ND	ND	ND	NM	NM	ND	ND	ND
M13	ND	ND	ND	ND	ND	ND	ND	NM	NM	ND	ND	ND
M14	ND	ND	ND	ND	ND	0.3	ND	NM	NM	ND	ND	ND
unknown	ND	ND	ND	ND	ND	0.3	ND	NM	NM	ND	30 (0.21)	ND
study	1041579			1041579			1039931			NP25158		

Excretion

The major route of elimination in rats was biliary excretion since 98.1% of 14C-labeled vemurafenib (MBP formulation) was recovered in feces. In an extended mass balance study a single intravenous or oral administration of [14C]-vemurafenib to naïve (without bile duct cannulation) or bile duct cannulated rats, the elimination of absorbed radioactivity was primarily hepatic. In naïve rats, the amount of radioactivity recovered in the feces was approximately 45- and 842-fold higher than that recovered in the urine after an intravenous and oral dose, respectively. In animals with implanted bile duct catheters, the amount of administered radioactivity recovered in the bile was approximately 25- and 58-fold higher than that recovered in the urine following intravenous and oral dose, respectively. Elimination of total radioactivity was not complete at 24 hours post dose in both naïve rats or animals with implanted bile duct catheters.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity studies were performed in rats and dogs. Studies were non-GLP. The results are shown in Table 5.

Table 5 Single dose toxicity studies with vemurafenib

Study ID	Species/ Sex/Number/ Group	Dose/Route (mg/kg)	Approx. lethal dose / observed max non-lethal dose	Major findings
GT 05120	Rat 3M/gp	30, 100, 300, 1000 oral gavage	None/1000	≥30: body weight ↓
WIL 578001	Dog 1/sex/gp	100, 300, 1000 (single escalating) or 100 (4-day repeat) oral gavage	None/1000	≥100: injected sclera eye

Repeat dose toxicity

Repeat dose toxicity studies were performed in rats and dogs. The results are shown in Table 6.

Table 6 Repeated dose toxicity studies with vemurafenib

Study ID	Species/Sex/ Number/Group	Dose/Route (mg/kg/day)	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
GT-06042/ 1040818	Rat 3 M/gp	0, 30, 300, 1000, 2000 Oral gavage	4 days	NOEL 300	≥1000: cholesterol ↑
GT-06019/ 1040816	Rat 5 M/gp	30, 100, 300 oral gavage	5 days	NOEL 300	None
GT-05132/ 1040815	Rat 6 M/gp	0, 30, 200, 600 oral gavage	13 days	NOEL 600	None
WIL578004/ 1040820	Rat 10-16/sex/gp among which 6/sex/gp of control and high dose for recovery Toxicokinetics 3 or 9/sex/gp	0, 30, 100, 1000 oral gavage	28 days 14 days recovery	NOEL 30	≥100: lymphangiectasis in jejunum 1000: cholesterol ↑, corneal crystals, heart weight ↑, heart minimal chronic inflammation
10165/ 1025760	Rat 36/sex/gp (among which 10/sex/gp for 13 week sacrifice and 6-8/sex/gp for recovery	0, 10, 50, 450 oral gavage	13 or 26 weeks 12 weeks recovery	NOEL 50	450: cholesterol ↑ (after 26 weeks), F: uterus dilatation (after 26 weeks)
WIL578003/ 1040819	Dog 3-5/sex/gp among which 2/sex/gp of control and high dose gp for recovery	0, 30, 100, 1000 oral gavage	28 days 14 days recovery	NOAEL 100	≥100: soft feces 1000: emesis, M: cholesterol ↑, F: injected sclera eye, food cons.↑
11025/ 1033163	Dog 6/sex/gp	0, 50, 150, 450/300* BID Oral gavage	37 days	< 100	≥100: vomiting, salivation, F: cholesterol ↑ ≥300: food cons.↓, ALT, AST, ALP, GGT ↑, triglycerides ↑, M: cholesterol ↑, F: glucose ↓ ≥600: bw loss, hypoactivity, body temp ↑, dehydration, WBC ↑ (mono, EOS, neut) 900: sacrificed prematurely, bone marrow necrosis, liver degeneration

Study ID	Species/Sex/ Number/Group	Dose/Route (mg/kg/day)	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
11260/ 1032862	Dog 6-9/sex/gp (among which 2-3/sex/gp for 4 week sacrifice and 2/sex/gp for recovery	0, 75, 150 BID oral gavage	4 or 13 weeks 4 weeks recovery	< 150	≥150: ALT, ALP, GGT ↑, liver perivascular mixed infiltrates + Kupffer cells, vomiting, WBC ↑, cholesterol ↑, kidney papillary mineralization, F: premature sacrifice 300: bw + food cons.↓, EOS ↑, degenerative changes liver, M: premature sacrifice, F: glucose ↓
10164/ 1025759	Dog 5/sex/gp (among which 2/sex/gp for recovery)	0, 30, 150, 450 oral gavage	13 weeks 4 weeks recovery	NOEL 150	450: ALT ↑, F: vomiting

Bw: body weight

*: high dose animals received 450 mg BID on days 1-10 and 300 mg BID on days 19-37.

Genotoxicity

Genotoxicity studies were performed *in vitro*. The results are presented in Table 7.

Table 7 Genotoxicity studies

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria, AB29FU.503.BTL-RR1040822, GLP	Salmonella strains, TA 1535, TA 1537, TA 98, TA 100, Escherichia coli WP2 uvrA	1.5-5000 μg/plate, +/- S9 (Aroclor 1254-induced rat)	There was no evidence of mutagenic activity following vemurafenib exposure in this study.
Gene mutations in bacteria, 2235M07-RR1026775, GLP	*S. typhimurium*, TA1535, 97, 98, 100, 102	50-5000 μg/plate, +/- S9 (5,6-benzoflavone treated animals)	Precipitation in the aqueous medium was observed at concentrations > 158 µg/plate (plate incorporation assay) and > 63.3 (preincubation assay). Toxic effects were not apparent. No increase in the number of revertant colonies was apparent for any of the five tester strains after treatment with vemurafenib.
Chromosome Aberrations in Human Lymphocytes Cultured "*in vitro*" , Study AB29FU.341.BTL.RR1040821, GLP	Human lymphocytes from healthy donors.	3.13-50 µg/mL, +/- S9 (aroclor 1254-induced rat)	Three independent tests were conducted. One test used a 4-hour treatment period (no metabolic activation), followed by a 16-hour recovery period. The second test used a 20-hour treatment period (no metabolic activation) with no

			recovery. The last test used a 4-hour treatment period with metabolic activation, followed by a 16-hour recovery period. No induction of structural or numerical chromosome aberrations was noted in this study.
Micronucleus Test in Mouse Bone Marrow, Study 10263-RR1026332, GLP	Male and female Hsd:SD mice treated by oral gavage (single dose)	30, 150, 800 mg/kg, MBP formulation	Bone marrow was collected at 24 and 48 hrs post-dose and bone marrow cells [polychromatic erythrocytes (2000 PCEs/animal)] were examined microscopically for the presence of micronuclei (micronucleated PCEs). Vemurafenib did not induce a statistically significant increase in the incidence of micronucleated PCEs. Cyclophosphamide monohydrate, the positive control at a dose of 40 mg/kg, induced a statistically significant increase in the incidence of micronucleated PCEs in both male and female rats.

Carcinogenicity

There were no carcinogenicity studies submitted by the applicant.

Reproduction Toxicity

Reproduction toxicity was investigated in several studies in rats and rabbits. The major findings and NOAEL results are presented in Table 8.

Table 8 Reproduction toxicity studies

Study type/ Study ID / GLP	**Species; Number Female/ group**	**Route & dose**	**Dosing period**	**Major findings**	**NOAEL (mg/kg &AUC)**
Embryo-fœtal development (dose-range finding)/ 1026029/ non-GLP	Pregnant rats 8F/gp + 6F/gp for toxicokinetics	0, 30, 150, 800 mg/kg/day (in 2% Klucel LF pH4) oral gavage	GD 6- 17 Sacrifice GD 20	F0: 800: bw gain ↓, food cons.↓ F1: none	**F0:** 150 $AUC_{(0\text{-}24h)}$: day 1: 460 µg*h/mL day 12: 790 µg*h/mL **F1**: 800 $AUC_{(0\text{-}24h)}$: day 1: 1680 µg*h/mL day 12: 3120 µg*h/mL
Embryo-fœtal development/ 1028543/ GLP	Pregnant rats 25F/gp + 3-6F/gp for toxicokinetics	0, 30, 100, 250 mg/kg/day (in 2% Klucel LF pH4) oral gavage	GD 6-17 Sacrifice GD 20	F0: none F1: none	**F0:** 250 $AUC_{(0\text{-}24h)}$: day 1: 789 µg*h/mL day 12:

					1590 µg*h/mL **F1:** 250
Embryo-fœtal development (dose-range finding)/ 1026033/ non-GLP	Pregnant rabbits 6F/gp + 3F/gp for toxicokinetics	0, 30, 150, 450 mg/kg/day (in 2% Klucel LF pH4) oral gavage	GD 7-20 Sacrifice GD 29	F0: 450: labored respiration F1: none	**F0**: 150 $AUC_{(0-24h)}$: day 1: 272 µg*h/mL day 14: 477 µg*h/mL **F1**: 150 #
Embryo-fœtal development/ 1028544/ GLP	Pregnant rabbits 22F/gp + 3F/gp for toxicokinetics	0, 30, 150, 450 mg/kg/day (in 2% Klucel LF pH4) oral gavage	GD 7-20 Sacrifice GD 29	F0: 450: bw gain ↓, food cons.↓ F1: none	**F0:** 150 $AUC_{(0-24h)}$: day 1: 194 µg*h/mL day 14: 577 µg*h/mL **F1:** 450 $AUC_{(0-24h)}$: day 1: 342 µg*h/mL day 14: 674 µg*h/mL

GD: gestation day; Bw: body weight; #: At 450 mg/kg, foetuses could not be evaluated due to maternal deaths caused by dosing errors on gestation days 9-11.

Toxicokinetic data

There were no toxicokinetic studies submitted by the applicant.

Local Tolerance

There were no local tolerance studies submitted by the applicant.

Other toxicity studies

Phototoxicity

Vemurafenib absorbed UV light significantly between 240 nm and 450 nm. Therefore, vemurafenib was assessed for possible phototoxic potential *in vitro* by the 3T3 fibroblast Neutral Red uptake assay. Vemurafenib was tested at concentrations ranging from 0.004 to 9.000 µg/mL. Absorption was measured at 540 nm. IC50 was determined to be >9 µg/mL for the non-irradiated (DARK) cytotoxicity control and 0.197 µg/mL for UVA irradiated cells. The DARK/UVA photoirritation factor for phototoxicity was determined to be ≥45.6. Applying the threshold photoirritation factor value of 5 (determined in validation studies for predicting *in vivo* activity), vemurafenib was shown to be phototoxic *in vitro* in cultured murine fibroblasts after UVA irradiation.

Phototoxicity of vemurafenib was assessed *in vivo* in the hairless rat study. Vemurafenib (MBP formulation) was administered orally by gavage to female hairless rats (6/group) at 0, 30, 150 or 450 mg/kg/day for 7 days. Vemurafenib did not appear to induce phototoxic skin reactions up to 450 mg/kg/day in animal models.

Haemotoxicity

An *in vitro* bone marrow cytotoxicity study was conducted to examine the potential for direct cytotoxic effect of vemurafenib on the bone marrow. Vemurafenib was tested at concentrations ranging from 0.75 to 125 μM, in 7 different lympho-hematopoietic cells from rat, dog, or human bone marrow. Inhibition of proliferation was observed at concentrations higher than 15.6 μM, 62.5 μM and 31.3 μM in human, dog and rat cells respectively.

2.3.5. Ecotoxicity/environmental risk assessment

The applicant submitted an environmental risk assessment (ERA). Vemurafenib was shown not to be persistent, bioaccumulative and toxic (PBT/vPvB) for the environment. Risks to the sediment and soil compartment were deemed acceptable. For surface water, groundwater and the STP, a direct risk has not been demonstrated. A summary of the main studies submitted for the ERA are shown in Table 9.

Table 9 Summary of main environment risk assessment study results

Substance (INN/Invented Name): vemurafenib			
CAS-number: 918504–65–1			
PBT screening		Result	
Bioaccumulation potential- log K_{ow}	OECD117	log K_{ow} 4.74 at pH 5	
		log D_{ow} 3.80 at pH 7	
		log D_{ow} 3.26 at pH 9	
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	4.74	
	BCF	16.9-35.9 L/kg (parent,5% lipid)	not B
Persistence	DT50 or ready biodegradability	not readily biodegradable, not inherently biodegradable	
	DT50 soil (20°C)	>1000 d	vP
	DT50 water/sediment (20°C)	> 417 d and > 1000 d	vP
Toxicity	NOEC and CMR		see below
PBT-statement:	vemurafenib is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined F_{pen}	3.61	µg/L	> 0.01 threshold
Water solubility	2.71±0.44	µg/L	
Other concerns (e.g. chemical class)	no evidence for mutagenicity and reprotoxicity, not tested for carcinogenicity as it concerns an anti-cancer drug		No CM concerns, R not investigated
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 40137 L/kg	sandy loam soil
	OECD 106	K_{oc} = 44622 L/kg	loam soil
	OECD 106	K_{oc} = 45226 L/kg	loam soil
	OECD 106	K_{oc} = 3739 L/kg	sewage sludge
	OECD 106	K_{oc} = 15701 L/kg	sewage sludge
Inherent Biodegradability Test (modified MITI test)	OECD 302	not readily biodegradable not inherently biodegradable	no degradation
Aerobic and Anaerobic	OECD 308	$DT_{50, water}$ < 2 d	vP

Transformation in Aquatic Sediment systems		$DT_{50,\ whole\ system}$ > 1000 d and 417 d 70-80% shifting to sediment from day 13 – 98			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test *P. subcapitata*	OECD 201	NOEC	> S_w (0.73)	mg/L	270 times higher than aqueous solubility
D. magna, acute toxicity	OECD 202	LC50	n.d.		no effects, but all concentrations < LOQ. Result unquantifiable
Daphnia sp. Reproduction Test	OECD 211	NOEC	> S_w (0.018)	mg/L	7 times higher than aqueous solubility
Fish, acute toxicity *P. reticulata*	OECD 203	LC50	n.d.		no effects, but all concentrations < LOQ. Result unquantifiable
Fish, Early Life Stage Toxicity Test/ *D. rerio*	OECD 210	NOEC	> S_w (≥ 1.63)	mg/L	higher than aqueous solubility
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	> S_w (≥ 301)	mg/L	higher than aqueous solubility
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	47.0-98.4	L/kg_{ww}	
Aerobic and anaerobic transformation in soil	OECD 307	DT50	> 1000	d	persistent in all four soils tested
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	EC10	604	mg/kg	nitrate formation, normalised to 2% o.c.
Terrestrial Plants, Growth Test *A. sativa*, *C. sativus*, *L. lycopersicum*	OECD 208	NOEC	638	mg/kg	shoot weight and length; normalised to 2% o.c.
Earthworm, Chronic Test *E. fetida*	OECD 222	NOEC	≥ 833	mg/kg	survival, growth, reproduction; normalised to 2% o.c.
Collembola, Reproduction Test *F. candida*	ISO 11267	NOEC	≥ 833	mg/kg	mortality and reproduction; normalised to 2% o.c.
Sediment dwelling organism *C. riparius*	OECD 218	NOEC	2381	mg/kg_{dw}	normalised to 10% o.c.
Sediment dwelling organism *L. variegatus*	OECD 225	NOEC	1157	mg/kg_{dw}	normalised to 10% o.c.
Sediment dwelling organism *C. elegans*	ISO 10872:2010	NOEC	≥4762	mg/kg_{dw}	normalised to 10% o.c.

2.3.6. Discussion on non-clinical aspects

Vemurafenib is a low molecular weight, orally available, inhibitor of BRAF serine-threonine kinase. Mutations in the BRAF gene which substitute the valine at amino acid position 600 result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation.

Preclinical data generated in biochemical assays demonstrated that vemurafenib can potently inhibit BRAF kinases with activating codon 600 mutations.

The inhibitory effect of vemurafenib on activated mutated BRAF was confirmed in the ERK phosphorylation and cellular anti-proliferation assays in available melanoma cell lines expressing V600-mutant BRAF. In cellular anti-proliferation assays the IC50 against V600 mutated cell lines (V600E, V600R, V600D and V600K mutated cell lines) ranged from 0.016 to 1.131 μM whereas the inhibitory concentration 50 against BRAF wild type cell lines were 12.06 and 14.32 μM, respectively. Vemurafenib was also found to inhibit activity of other kinases including RAF1, ARAF, BRK(PTK6), SRMS and ACK1.

BRAFWT cell lines treated with vemurafenib showed a dose-response increase in phosphorylation of ERK and MEK. This is an important finding as it may provide on one hand a hypothetical mechanism for the increase rate of cutaneous squamous cell carcinoma (cuSCC) which has been observed in clinical studies with vemurafenib and on the other hand a possible mechanism for acquired resistance. It has been speculated that upregulation of pERK might be a potential mechanism by which vemurafenib stimulates tumour growth in the A431 cuSCC model.

The preclinical safety profile of vemurafenib was assessed in rats, dogs, and rabbits. The non-clinical studies submitted were considered acceptable.

Repeat-dose toxicology studies identified the liver and bone marrow as target organs in the dog. Reversible toxic effects (hepatocellular necrosis and degeneration) in the liver at exposures below the anticipated clinical exposure (based on AUC comparisons) were noted in the 13-week dog study. Focal bone marrow necrosis was noted in one dog in a prematurely terminated 39-week BID dog study at exposures similar to the anticipated clinical exposure (based on AUC comparisons). In an *in vitro* bone marrow cytotoxicity study, slight cytotoxicity was observed in some lympho-hematopoietic cell populations of rat, dog and human at clinically relevant concentrations.

There were no safety signals observed in the *in vivo* safety pharmacology core battery studies performed in dog and rat.

No specific studies with vemurafenib have been conducted in animals to evaluate the effect on fertility. However, in repeat-dose toxicity studies, no histopathological findings were noted on reproductive organs in males and females in rats and dogs at doses up to 450 mg/kg/day (at exposures below the anticipated clinical exposure based on AUC comparison). No teratogenicity was observed in embryofoetal development studies in rats and rabbits at doses up to respectively 250 mg/kg/day and 450 mg/kg/day leading to exposures below the anticipated clinical exposure (based on AUC comparison). However, exposures in the embryofoetal development studies were below the clinical exposure based on AUC comparison, it is therefore difficult to define to what extent these results can be extrapolated to humans. Therefore an effect of vemurafenib on the foetus cannot be excluded. No studies were performed regarding pre- and postnatal development.

No signs of genotoxicity were identified in *in vitro* assays (bacterial mutation [AMES Assay], human lymphocyte chromosome aberration) nor in the *in vivo* rat bone marrow micronucleus test conducted with vemurafenib.

Carcinogenicity studies have not been conducted with vemurafenib. The lack of carcinogenic studies was acceptable since anti-neoplastic agents intended for treatment of advanced systemic disease do not generally need carcinogenicity studies according to current guidelines, ICH S1A and ICH S9 guideline.

Vemurafenib was shown to be phototoxic, *in vitro*, on cultured murine fibroblasts after UVA irradiation, but not *in vivo* in a rat study at doses up to 450 mg/kg/day (at exposures below the anticipated clinical exposure (based on AUC comparison). It is hypothesized that in the 7-day rat study, vemurafenib did

not reach the skin in a sufficient quantity to elicit a phototoxic response. The CHMP considered that the documentation was satisfactory and the photosensitivity signal was included in sections 4.4 and 4.8 of the SmPC.

The data presented by the applicant showed no direct toxicity against lympho-hematopoietic cells from the three different species tested.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical studies submitted for the marketing authorisation application for vemurafenib were considered adequate and acceptable for the assessment of non-clinical aspects for the product vemurafenib. The lack of carcinogenicity studies was justified and considered acceptable.

The CHMP requested to resolve some minor issues with regards to the consequences of the differences in organ distribution between animals and human and the extrapolation of the findings to humans and possibility of liver toxicity due to reactive metabolites. The CHMP requested the applicant to perform *in vitro* studies addressing this issue. These issues are covered in the RMP.

2.4. Clinical aspects

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitor, ATC code: L01XE15

2.4.1. Introduction

Using the criteria described in the Biopharmaceutics Classification System, vemurafenib was classified as a Class IV drug (low solubility and low permeability).

Vemurafenib is a Class IV substance (low solubility and permeability), using the criteria described in the Biopharmaceutics Classification System. The pharmacokinetic parameters for vemurafenib were determined using non compartmental analysis in a phase I and phase III studies (20 patients after 15 days of dosing at 960 mg twice daily, and 204 patients in steady state day 22) as well as by population PK analysis using pooled data from 458 patients. Among these patients, 457 were Caucasians.

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

Phase 1					
Protocol Number	**Study Objective**	**Study Design**	**Study Population**	**Dosing Regimen/Routes**	**No. of Patients Enrolled**
PLX06-02	Evaluate vemurafenib safety and PK determine maximum tolerated dose (MTD)	Open-label, dose escalation study followed by a treatment extension phase	**Dose Escalation** patients with solid tumours **Treatment Extension** Patients with *BRAF*^{V600}	**Dose Escalation** Original formulation: 200, 400, 800, and 1600 mg bid Micro-precipitated bulk powder (MBP) formulation (capsules): 160, 240, 320, 360, 720, 960, and 1120 mg	**Dose Escalation** Original Formulation n = 26 MBP Formulations n = 30

			mutation-positive melanoma and patients with *BRAF*^{V600} mutation-positive colorectal cancer	bid **<u>Treatment Extension</u>** MBP formulations (capsules and film-coated tablets): 960 mg bid	**<u>Treatment Extension</u>** *BRAF*^{V600} mutation-positive melanoma n = 32 *BRAF*^{V600} mutation-positive CRC n = 21 **TOTAL** n = 109
PLX102-01	Evaluate the relative bio-availability of two MBP formulations vs original crystalline formulation	Randomized, open-label, 3-period cross-over study	Male healthy volunteers	**Treatment A:** Reference original phase 1 crystalline formulation 900 mg (3 x 300 mg capsules), oral. Note: In period 3, this reference formulation was replaced with a new batch and dosed at 300 mg (3 x 100 mg capsules), oral **Treatment B:** MBP-1 (dry granulation) 160 mg (4 x 40 mg capsules), oral **Treatment C:** MBP-2 (wet granulation) 160 mg (4 x 40 mg capsules), oral	n = 18
NP22676	Evaluate the effect of vemurafenib on the PK of five CYP450 substrates given as a drug cocktail	Non-randomized, open-label, uncontrolled, multicenter study	Previously treated and untreated patients with *BRAF*^{V600} mutation-positive, stage IV metastatic melanoma	240 mg MBP film-coated tablets at 960 mg bid, oral **Period A (Days 1 – 6)**: Day 1: cocktail Days 1 to 6: washout **Period B (Days 6 – 19):** vemurafenib **Period C (Days 20 – 25):** Cocktail + vemurafenib **Period D (Day 26+):** vemurafenib	n = 25
NP25158	Characterize the mass balance, metabolism, routes and rates of elimination of	Non-randomized, open-label, uncontrolled, single centre study	Previously treated and untreated patients with BRAF^{V600}-mutation-positive	240 mg MBP film-coated tablets at 960 mg bid, oral Period A (Days 1 – 14): non-labelled vemurafenib	n = 7

	^{14}C-vemurafenib		unresectable Stage IIIc/IV melanoma	Period B (Day 15+): Single morning dose of radio labelled vemurafenib at 960 mg (6 X 120 mg capsules of unlabeled drug and 4 X 60 mg capsules each containing a maximum of 17.3 µCi of radioactive material) Evening dose of non-labelled vemurafenib 960 mg in 240 mg tablets Period C (after recovery criteria met) : non-labelled vemurafenib	
NP25163	Evaluate the PK of vemurafenib using the 240 mg MBP tablet formulation	Randomized, open-label, uncontrolled, multicenter study	Previously treated patients with $BRAF^{V600}$ mutation-positive unresectable Stage IIIc/IV melanoma	240 mg MBP film-coated tablets, oral Period A (Days 1 – 15) (Four vemurafenib dose cohorts): 240 mg bid 480 mg bid 720 mg bid 960 mg bid Period B (Days 16 – 21): Washout period Period C (Day 22+): 960 mg bid	n = 52 (n = 12 in each of Cohorts 1, 2 and 3; n = 16 in Cohort 4)
Phase 2					
NP22657	Evaluate efficacy (Best Overall Response rate (BORR)) of vemurafenib with substudy to assess QTc interval and vemurafenib exposure	Non-randomized, single-arm, open-label, uncontrolled, multicenter study	Previously treated patients with $BRAF^{V600}$ mutation-positive Stage IV melanoma	240 mg MBP film-coated tablets at 960 mg bid, oral	n = 132
Phase 3					
NO25026	Evaluate the efficacy (overall survival (OS) and progression free survival (PFS) of vemurafenib vs dacarbazine (dimethyl-triazenyl-imidazole-carboxamide) (DTIC) and assess PK of	Randomized, open-label, active-treatment controlled, multicenter study	Previously untreated patients with $BRAF^{V600}$ mutation-positive unresectable Stage IIIc/IV melanoma	RO5185246 group: 240 mg MBP film-coated tablets at 960 mg bid, oral DTIC group: IV 1000 mg/m2 Day 1 q3w	vemurafenib n = 337 DTIC n = 338

	240 mg film-coated tablets				

2.4.2. Pharmacokinetics

A summary of key pharmacokinetic parameters of vemurafenib is provided in Table 10.

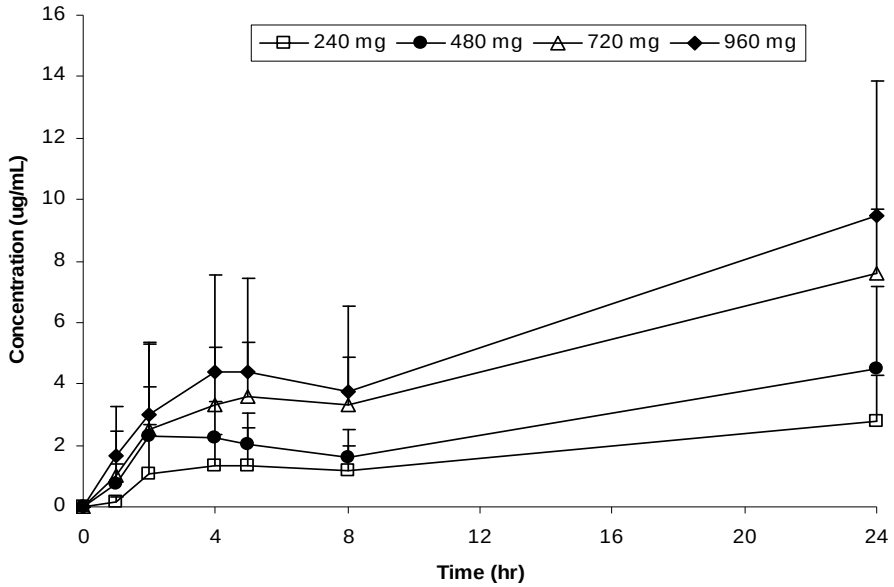
Table 10 Key pharmacokinetic parameters of vemurafenib

Absorption	The absolute bioavailability of vemurafenib is unknown. t_{max} = 4 hours Accumulation factor 15- to 17-fold for AUC_{0-8h}, and 13- to 14-fold for C_{max} upon multiple dosing of 960 mg BID
Distribution	V_d approximately 90 l. Binds >99% to proteins.
Metabolism	Substrate of CYP3A4 but parent drug is predominant in plasma
Excretion	$t_{1/2}$ approximately 56 hours Unclear how much is excreted hepatically or renally
Interactions	Inhibitor of CYP1A2 and 2C9, inducer of CYP3A4. Inhibitor and substrate of P-gp

Absorption

After p.o. administration of a single 960 mg dose of vemurafenib, the substance was absorbed with a t_{max} of approximately 4 h. Mean C_{max} at the 960 mg dose level was approximately 4.8 ± 3.3 µg/ml. A representative concentration-time curve is shown in Figure 7.

Figure 7 Mean (± SD) vemurafenib concentration vs time profile on day 1. – Study NP25163



- **Bioavailability**

An absolute bioavailability study was not performed. Due to the limited solubility of vemurafenib at physiological pH 6.8, (0.01-0.10 µg/ml), it was not possible to formulate standard doses as an intravenous formulation.

- **Influence of food**

An attempt to evaluate the effect of concomitant food on vemurafenib bioavailability was made in a substudy within Study PLX06-02. However, the substudy failed because of insufficient number of patients. A dedicated food effect study (NP25396) has been initiated with the final tablet formulation.

Distribution

As absolute bioavailability, F, is unknown, volume of distribution could only be estimated. In Study NP25163, the elimination rate constant K_{el} for the 960 mg dose was calculated to be 0.020/h with an estimated AUC_{tau} = $AUC_{0\text{-}12h}$ of 600 µg*h/mL. From these data, Vd/F (Dose/[$AUC_{0\text{-}tau}$ x k_{el}]) was estimated from steady-state values to be approximately 80 L.

The volume of distribution, based on the final population-PK model, was 91 l, with a between patient variability of 64.8%. Blood/plasma ratio for vemurafenib was 0.58, and was independent of vemurafenib concentration. In the mass-balance study NP25158, blood/plasma ratio for total radioactivity was 0.72 ± 0.05 (range, 0.69 to 0.81).

Elimination

The elimination rate constant and elimination half-life across the four dose cohorts in study NP25163 (240 mg to 960 mg bid) were assessed by the use of a 7-day drug interruption period after 15 days of dosing. The mean elimination half-life values were 31.5, 38.4, 34.9 and 34.1 hours for the 240, 480, 720 and 960 mg bid doses, respectively. Analysis of mean trough data following vemurafenib dose interruption indicates that 95% of the drug was cleared from the body in 7 days.

- **Excretion**

Mass-balance study

In study NP25158, identification of vemurafenib and metabolites in plasma, faeces and urine was made for the first 96 hr, with a total collection period of 432 hrs (18 days).

Mean data from the 7 patients indicated that over the period investigated (0 to 96 hours), potential metabolites each accounted for < 0.5% of the total administered dose in urine and ≤6% of the total administered dose in faeces. In pooled faecal samples up to 48 hours post post-dose, parent compound accounted for at least 94% of total radioactivity (37% of the dose).
In faecal samples taken 48-96 hr post-dose, the amount of metabolites increased, with M6, M3, and M8 representing approximately 19%, 14% and 12%, of the total chromatographic peak area, respectively (mean values) or 3%, 5% and 4% of the dose, respectively. Over the 0-96 hr collection period, potential metabolites M3 (mono-hydroxy) and M6 (glucosylation) each accounted for <0.5% of the total administered dose in urine. Vemurafenib accounted for approximately 1% of the total dose in urine.

Dose proportionality and time dependencies

In the population pharmacokinetic analysis, mean values for Cmax and Cmin at steady state after 960 mg BID dosing were 63.8 µg/ml and 61.0 µg/ml, respectively.

A dose escalation study, NP25163, was performed to characterise the pharmacokinetic profile of single- and multiple dose vemurafenib across the therapeutic dose range with the final 240 mg film-coated tablet for BID administration (Table 11 and 12).

Table 11 Pharmacokinetic parameters for vemurafenib in each dose cohort on Day 1 – Study NP25163

Dose	n	AUC 0-8 hr first dose (µg*h/ml)	Cmax first dose (µg/ml)	Tmax first dose (h)	AUC 0-24 hr second dose (µg*h/ml)
240 mg BID	12	8.3 (73.9%)	1.9 (85.3%)	4.0 (1.9 – 8.0)	40.9 (57.3%)[a]
480 mg BID	12	13.8 (55.8%)	2.6 (60.5%)	4.0 (1.9 – 5.0)	62.4 (57.2%)[b]
720 mg BID	12	21.9 (59.3%)	4.4 (44.6%)	5.0 (2.0 – 8.1)	111.6 (34.22%)
960 mg BID	16	27.0 (69.9%)	4.8 (69.8%)	5.0 (2.0 - 8.0)	130.6 (71.78%)

[a] n= 11; [b] n= 9; Parameters are presented as arithmetic mean (CV%) except Tmax, which is presented as median (range)

Table 12 Summary of vemurafenib exposure at Day 15 at doses from 240 to 960 mg bid – Study NP25163

	240 mg	480 mg	720 mg	960 mg
AUC_{0-8h} µg·h/mL				
N	10	9	9	11
Mean	117.8	223.8	343.3	392.2
SD	50.52	106.93	151.23	126.37
CV%	42.9	45.7	44.1	32.2
AUC_{0-24h} µg·h/mL				
N	10	10	9	11
Mean	317.7	598.8	1003.7	1126.0
SD	133.34	297.44	441.36	423.01
CV%	42.0	49.7	44.0	37.6
AUC_{0-168h} µg·h/mL				
N	10	8	9	11
Mean	920.3	2243.5	3127.1	3530.3
SD	538.35	1336.15	1789.97	1811.43
CV%	58.5	59.6	57.2	51.3
C_{max} µg/mL				
N	10	9	9	11
Mean	17.2	35.4	52.7	61.4
SD	7.43	17.44	22.40	22.76
CV%	43.1	49.2	42.5	37.1

A comparison of vemurafenib pharmacokinetic parameters on Day 1 and Day 15 in the Phase 2 Study NP22657 and the 960 mg bid cohort in Study NP25163 is shown in Table 13. The ratio between the mean values on Day 15 and Day 1 from both studies ranged from 15- to 17-fold for AUC_{0-8h}, and 13- to 14-fold for C_{max} (Table 17).

Table 13 Comparison of pharmacokinetic parameters on day 1 and day 15 (960 mg bid) – Studies NP22657 and NP25163

Parameters	NP22657		NP25163	
	Day 1	Day 15	Day 1	Day 15
AUC_{0-8h} [a] (µg·h/mL)	22.1 ± 12.7 (3.5–56.4, n=88)	380.2 ± 143.6 (66.2–903.9, n=87)	27.0 ± 18.9 (2.8–57.7, n=16)	392.2 ± 126.4 (217.3–575.7, n=11)

C_{max} [a] (µg/mL)	4.1 ± 2.3 (0.64–11.8, n=88)	56.7 ± 21.8 (10.2–118.0, n=87)	4.8 ± 3.3 0.61–10.7, n=16)	61.4 ± 22.8 [c] (31.2–106.0, n=11)
T_{max} [b] (h)	4 (1.8–8.1) n = 88	2 (0–8.9) n = 88	5 (2–8) n = 16	2 (0–24) [c] n = 11

[a] Mean ± SD, (Min–Max values, Number of patients evaluated).
[b] Median (Min-Max), Number of patients.
[c] Time interval of assessment equals 0-168 hours.

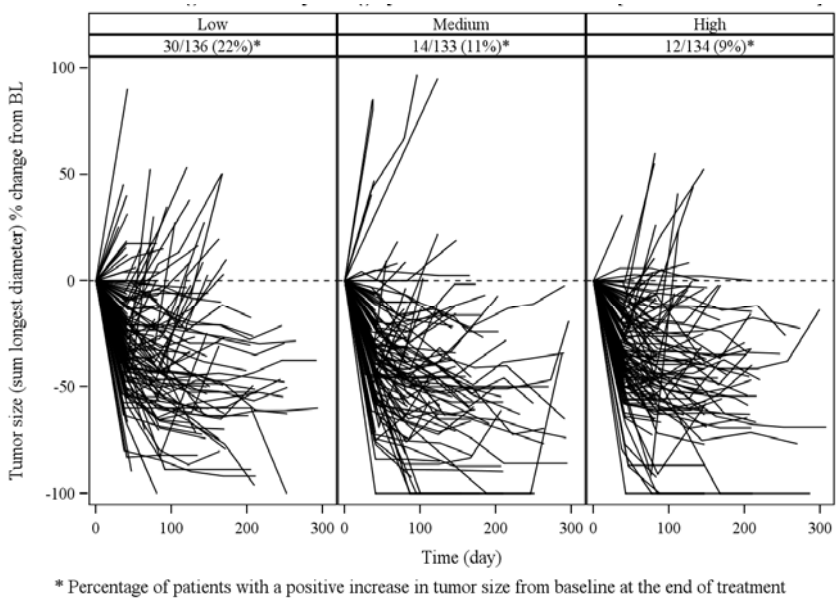
- Intra and Inter- variability

Across studies NP25163, NP22657, and NP22676, the inter-patient variability (CV%) for both AUC and Cmax at Day 1 (single dose) and Day 15 (multiple doses) were between 57.6% to 69.9% and 27.9% to 38.4%, respectively.

- Tumour size change with treatment

In a population PK/PD analysis, relationship between vemurafenib exposure and tumour size change from baseline, was investigated. There were three exposure categories of mean AUC that were defined: low, medium, and high. Significant reductions in tumour size over time were observed in all exposure categories. However, the percentage of patients with a positive increase in tumour size from baseline at the end of treatment was higher (22%) in the low exposure category than in the medium and high exposure categories (11% and 9%, respectively) (Figure 14).

Figure 14 Change in Tumour Size from Baseline by Three Categories of Mean AUC – Studies NP22657 and NO25026



* Percentage of patients with a positive increase in tumor size from baseline at the end of treatment

Special populations

The covariate "gender" was found to statistically influence the CL/F and the V/F, with a 17% greater CL/F and a 48% greater V/F in male patients in the population pharmacokinetic analysis. Mean vemurafenib exposure (AUC_{0-8h} on Day 15) was approximately 42% higher in female than male patients.

Body weight and age was not a statistically significant co-variate in the population PK analysis.
The applicant did not submit studies in children.

There were no studies submitted in renal impaired patients and in hepatic impaired patients.

There were no pharmacokinetic data submitted in children.

Pharmacokinetic interaction studies

Vemurafenib concentrations up to 50 µM were used in PK interaction studies. The results showed that vemurafenib has a potential to inhibit the activity of CYP2C9, CYP2D6, CYP1A2, CYP2C19, and CYP3A4/5, the IC50 were 5.9 µM, 33.2 µM, 32.5 µM and 22.5 µM, respectively. For CYP2A6, 2E1 and 3A4 no significant inhibition was seen at concentrations up to 50 µM. No time-dependent irreversible inhibition of CYP3A4 was detected (24 minutes pre-incubation).

Vemurafenib did not induce CYP3A4/5 activity at concentrations up to 10 µM in *in vitro* induction studies using human hepatocytes.

In vitro results showed that vemurafenib is a weak P-gp substrate. The calculated IC_{50} was 17 and 3.5 µM for digoxin and quinidine, respectively. The efflux ratio was decreased from 5.0 at 10 µM to 1.8 and 1.1 at 25 and 50 µM, respectively.

Vemurafenib was neither a substrate nor an inhibitor for OATP1B1 and OATP1B3 (Study 11707-RR1041536) up to a concentration of 50 µM.

The effect of vemurafenib on several CYP enzymes is summarised in Table 15.

Table 15 Effect of vemurafenib 960 mg bid at steady state on the AUC and metabolic ratio of five probe drugs (single dose)

Enzyme	Parameter	Treatment Period A (test drug alone)		Treatment period C (test drug + vemurafenib)	
		Parent (P)	**Metabolite (M)**	**Parent (P)**	**Metabolite (M)**
CYP1A2		*caffeine*	*paraxanthine*	*caffeine*	*paraxanthine*
	$AUC_{0\text{-last}}$ (ng*hr/ml)	56350	45584	140991	51344
	CL/F (ml/hr)	4.2	N/A	1.6	N/A
	P/M mean ratio for AUC	1.34		4.09	
	PeriodC/PeriodA mean ratio for P/M ratio and 90% CI	0.33 (0.27-0.40)			
CYP2D6		*dextromethorphan*	*dextrorphan*	*dextromethorphan*	*dextrorphan*
	$AUC_{0\text{-last}}$ (ng*hr/ml)	28.4	26.8	39.33	37.7
	CL/F (ml/hr)	4108	N/A	2922	N/A
	P/M mean ratio for AUC	0.56		0.56	
	PeriodC/PeriodA mean ratio for P/M ratio and 90% CI	0.99 (0.80 - 1.24)			
CYP3A4		*midazolam*	*hydroxymidazol*	*midazolam*	*hydroxymidazol*
	$AUC_{0\text{-last}}$ (ng*hr/ml)	100.2	43.0	67.7	59.8
	CL/F (ml/hr)	72200	N/A	125437	N/A
	P/M mean ratio for AUC	2.32		1.04	
	PeriodC/PeriodA mean ratio for P/M ratio and 90% CI	2.22 (1.86 - 2.65)			
CYP2C19		*omeprazole*	*OH - omeprazole*	*omeprazole*	*OH - omeprazole*
	$AUC_{0\text{-last}}$ (ng*hr/ml)	3110	1187	3155	1370
	CL/F (ml/hr)	0.035	N/A	0.027	N/A
	P/M mean ratio for AUC	1.64		1.59	
	PeriodC/PeriodA mean ratio for P/M ratio and 90% CI	1.03 (0.88 - 1.21)			
CYP2C9		S - warfarin			
	$AUC_{0\text{-last}}$ (ng*hr/ml)	14964	N/A	17804	N/A
	CL/F (ml/hr)	622	N/A	514	N/A

2.4.3. Pharmacodynamics

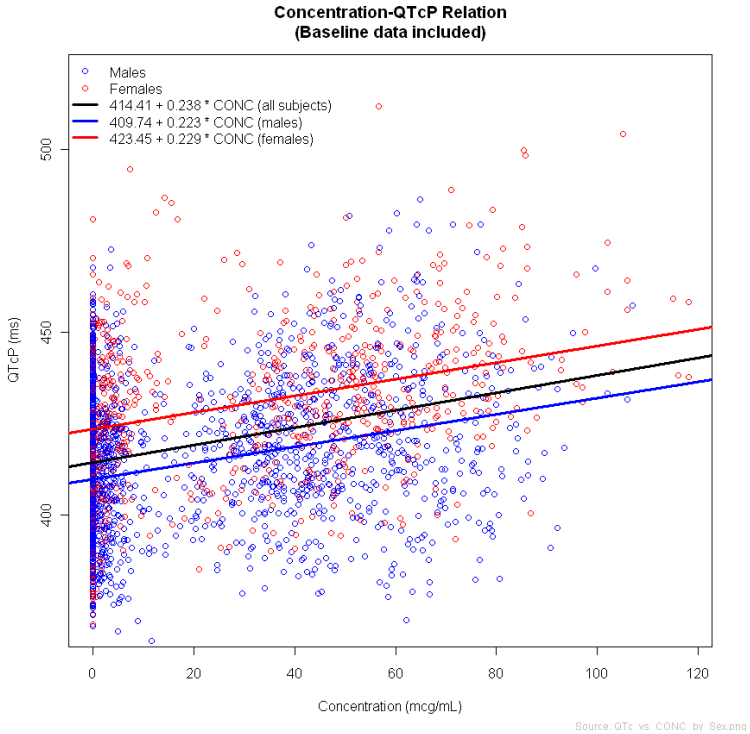
Mechanism of action

The applicant did not submit clinical studies on mechanism of action.

Primary and Secondary pharmacology

The applicant investigated the dependence of time-matched QTcP changes from baseline on vemurafenib concentrations. The results are shown in Figure 8.

Figure 8 Relationship between vemurafenib concentration and Observed QTcP



2.4.4. Discussion on clinical pharmacology

Vemurafenib is a Biopharmaceutics Classification System (BCS) Class IV drug (low solubility and permeability). The applicant did not conduct an absolute bioavailability study. This was considered acceptable since vemurafenib has low solubility in physiological solutions of pH 6.8 (0.01-0.10 µg/mL). Given the risk for cutaneous squamous cell carcinoma, it was also considered acceptable that volunteers were not used in any of the Pk/PD studies.

The effect of food on absorption of vemurafenib is currently unknown. Variability in exposure may occur due to differences in gastro-intestinal fluid content, volumes, pH, motility and transition time and bile composition.

At steady state, the mean vemurafenib exposure in plasma is stable during the 24-hour interval as indicated by the mean ratio of 1.13 between the plasma concentrations before and 2-4 hours after the morning dose.

Following oral dosing, the absorption rate constant for the population of metastatic melanoma patients is estimated to be 0.19 hr^{-1} (with 101% between patient variability).

A dedicated food effect study was not performed during the clinical development. The lack of food effect data was accepted as the clinical benefit had been demonstrated. The CHMP requested the applicant to submit the data from the ongoing food effect study NP25396 to further study the association between concomitant intake of food may and the absorption of vemurafenib. This post-authorisation measure is covered in the RMP. The current recommendation in the SmPC is that each dose in the morning/evening should always be taken in the same manner i.e. either with or without a meal (SmPC section 4.2).

Relationship between vemurafenib exposure and tumour size change from baseline was investigated. The CHMP highlighted that the risk of underexposure to vemurafenib could affect reduction of tumour size and, as a consequence, decrease efficacy. The CHMP requested the applicant to perform a study to analyse patients that may have low exposure. The study has been included in the RMP and will be covered by the ongoing food effect study NP25396 with results expected by June 2012.

Vemurafenib is highly protein bound (>99%) and appears to be a Pgp substrate but is not a substrate of OATP1B1 and OATP1B3. The CHMP requested the applicant to perform an interaction study with digoxin (see further in the conclusions). This post-authorisation measure is covered in the RMP.

The absolute bioavailability of the vemurafenib 240 mg tablet is unknown.
Vemurafenib at 960 mg twice daily is absorbed with a median Tmax of approximately 4 hours. Vemurafenib exhibits high inter-patient variability. In the phase II study, $AUC_{0\text{-}8h}$ and C_{max} at day 1 were 22.1 ± 12.7 µg·h/mL and 4.1 ± 2.3 µg/mL. Accumulation occurs upon multiple twice daily dosing of vemurafenib. In the non compartmental analysis, after dosing with 960 mg vemurafenib twice daily the Day 15 / Day 1 ratio ranged from 15- to 17-fold for AUC, and 13- to 14-fold for C_{max}, yielding $AUC_{0\text{-}8h}$ and C_{max} of 380.2 ± 143.6 µg·h/mL and 56.7 ± 21.8 µg/mL, respectively, under steady-state conditions.
Vemurafenib is the major circulating compound in plasma, accounting for 95% of the drug-related material.

The population apparent volume of distribution for vemurafenib in metastatic melanoma patients is estimated to be 91 L (with 64.8% between patient variability). It is highly bound to human plasma proteins *in vitro* (>99%).
The relative proportions of vemurafenib and its metabolites were characterized in a human mass balance study with a single dose of ^{14}C-labeled vemurafenib administered orally. CYP3A4 is the primary enzyme responsible for the metabolism of vemurafenib *in vitro*. Conjugation metabolites (glucuronidation and glycosylation) were also identified in humans. However, the parent compound was the predominant component (95%) in plasma. Although metabolism does not appear to result in a relevant amount of metabolites in plasma, the importance of metabolism for excretion cannot be excluded.
Elimination of vemurafenib is slow and population pharmacokinetic data indicate a half-life of approximately 50 hr. With twice daily dosing (BID), accumulation of the parent compound is large, about 20 to 25-fold, and there is virtually no fluctuation in plasma concentrations over the dosing interval at steady state. Pharmacokinetic data for up to 15 days indicate that steady state is not reached in all patients on Day 15. It will also take more than two weeks to washout the substance after cessation of treatment, or to have full effect of a potential dose adjustment. Accordingly management of symptomatic adverse drug reactions or QTc prolongation may require dose reduction, temporary interruption and/or treatment discontinuation (see table 16). Posology adjustments resulting in a dose below 480 mg twice daily are not recommended. These recommendations are reflected in the SmPC.

In the event the patient develops Cutaneous Squamous Cell Carcinoma (cuSCC), it is recommended to continue the treatment without modifying the dose of vemurafenib (see sections 4.4 and 4.8 of the SmPC).

Table 16: Dose modification schedule based on the grade of any AEs

Grade (CTC-AE) [(a)]	**Recommended dose modification**
Grade 1 or Grade 2 (tolerable)	Maintain vemurafenib at a dose of 960 mg twice daily.
Grade 2 (intolerable) or Grade 3	
1st occurrence of any grade 2 or 3 AE	Interrupt treatment until grade 0 – 1. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).
2nd occurrence of any grade 2 or 3 AE or persistence after treatment interruption	Interrupt treatment until grade 0 – 1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
3rd occurrence of any grade 2 or 3 AE or persistence after 2nd dose reduction	Discontinue permanently.
Grade 4	
1st occurrence of any grade 4 AE	Discontinue permanently or interrupt vemurafenib treatment until grade 0 – 1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
2nd Occurrence of any grade 4 AE or persistence of any grade 4 AE after 1st dose reduction	Discontinue permanently.

[(a)] The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE).

Exposure-dependent QT prolongation was observed in an uncontrolled, open-label phase II study in previously treated patients with metastatic melanoma. Management of QTc prolongation may require specific monitoring measures (see section 4.4 of the SmPC) (Table 17).

Table 17: Dose modification schedule based on prolongation of the QT interval

QTc value	**Recommended dose modification**
QTc>500 ms at baseline	Treatment not recommended.
QTc increase meets values of both > 500 ms and >60 ms change from pre-treatment values	Discontinue permanently.
1st occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60 ms	Temporarily interrupt treatment until QTc decreases below 500 ms. See monitoring measures in section 4.4. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).
2nd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60ms	Temporarily interrupt treatment until QTc decreases below 500 ms. See monitoring measures in section 4.4. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
3rd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60ms	Discontinue permanently.

No special dose adjustment is required in patients aged > 65 years old.

The population apparent clearance of vemurafenib in patients with metastatic melanoma is estimated to be 29.3 L/day (with 31.9% between patient variability). The population elimination half-life estimated by the population PK analysis for vemurafenib is 51.6 hours (the 5th and 95th percentile range of the individual half life estimates is 29.8 - 119.5 hours).

In the human mass balance study with p.o.vemurafenib administered orally vemurafenib, on average 95% of the dose was recovered within 18 days. The majority of vemurafenib-related material (94%) was recovered in faeces, and <1% in urine. Biliary excretion of unchanged compound may be an important route of elimination. However, due to the unknown absolute bioavailability, the importance of hepatic and renal excretion for the clearance of parent vemurafenib is uncertain.

The majority of drug-related material was excreted in faeces. Without absolute bioavailability data, the relative importance of metabolism vs. biliary excretion of unchanged parent compound cannot be definitely concluded. The CHMP as recommended that the applicant performs an absolute bioavailability study to gather more information on the metabolism and biliary excretion of vemurafenib. However, based on the available data, biliary excretion could account for about 60% of the elimination and metabolism for 40%. The metabolism appears to be primarily via three, approximately equally important pathways: CYP3A4, glucuronidation (UGT not identified) and glucosylation.

Elderly

Based on the population PK analysis, age has no statistically significant effect on vemurafenib pharmacokinetics.

Gender

The population pharmacokinetic analysis indicated a 17% greater apparent clearance (CL/F) and a 48% greater apparent volume of distribution (V/F) in males than in females. It is unclear whether this is a gender or a body size effect. However, the differences in exposure are not large enough to warrant dose adjustment based on body size or gender.

Paediatric population

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

Renal impairment

In the population pharmacokinetic analysis using data from clinical trials in patients with metastatic melanoma, mild and moderate renal impairment did not influence the apparent clearance of vemurafenib (creatinine clearance >40 ml/min). There are no data in patients with severe renal impairment (see sections 4.2 and 4.4). There was no study in renal impaired patients submitted with the application. Although renal excretion is likely to be of minor importance for the elimination of vemurafenib, patients with severe renal impairment who are not on dialysis may be at risk of increased levels of urinary toxins that could have the potential to inhibit certain transporters. A warning has been included in the SmPC in section 4.4 that limited data are available in patients with renal impairment. A risk for increased exposure in patients with severe renal impairment cannot be excluded. Patients with severe renal impairment should be closely monitored (see sections 4.4 and 5.2).

Hepatic impairment

Based on preclinical data and the human mass balance study, major part of vemurafenib is eliminated via the liver. In the population pharmacokinetic analysis using data from clinical trials in patients with metastatic melanoma, increases in AST and ALT up to three times the upper limit of normal did not influence the apparent clearance of vemurafenib. Data are insufficient to determine the effect of metabolic or excretory hepatic impairment on vemurafenib pharmacokinetics (see sections 4.2 and 4.4). There was no study in hepatic impaired patients submitted with the application. A warning has been included in the SmPC to the effect that limited data are available in patients with hepatic impairment. As vemurafenib is cleared by the liver, patients with moderate to severe hepatic

impairment may have increased exposure and should be closely monitored (see sections 4.4 and 5.2 of the SmPC). The CHMP requested the applicant to perform a study on severe hepatic impaired patients. This post-authorisation measure is covered in the RMP.

The safety and efficacy of vemurafenib has not been yet established in children and adolescents (<18 years). No data are available.

The safety and efficacy of vemurafenib has not been established in non-Caucasian patients. No data are available.

Effects of vemurafenib on CYP substrates

CYP1A2 inhibition was observed when a single dose of caffeine was co-administered after repeat dosing with vemurafenib for 15 days. This resulted in an average 2.5-fold increase (maximum up to 10-fold) in caffeine plasma exposure after vemurafenib treatment. Vemurafenib may increase the plasma exposure of substances predominantly metabolized by CYP1A2 and dose adjustments should be considered.

CYP3A4 induction was observed when a single dose of midazolam was co-administered after repeat dosing with vemurafenib for 15 days. This resulted in an average 32% decrease (maximum up to 80%) in midazolam plasma exposure after vemurafenib treatment. Vemurafenib may decrease the plasma exposure of substances predominantly metabolized by CYP3A4. On this basis, the efficacy of contraceptive pills metabolized by CYP3A4 used concomitantly with vemurafenib might be decreased. Dose adjustments for CYP3A4 substrates with narrow therapeutic window should be considered (see section 4.4 and 4.6).

Mild induction of CYP2B6 by vemurafenib was noted *in vitro* at a vemurafenib concentration of 10 µM. It is currently unknown whether vemurafenib at a plasma level of 100 µM observed in patients at steady state (approximately 50 µg/ml) may decrease plasma concentrations of concomitantly administered CYP2B6 substrates, such as bupropion. The CHMP requested the applicant to perform *in vitro* studies for inhibition of CYP 2A6, 2E1, 2C8 and 2B6. This is currently adequately addressed in the SmPC. This post-authorisation measure is covered in the RMP.

When a single dose of warfarin was co-administered after repeat dosing with vemurafenib for 15 days, some patients exhibited increased warfarin exposure (mean 20%) (see section 4.4). Caution should be exercised when vemurafenib is co-administered with warfarin (CYP2C9) in patients with melanoma.

Due to the long half-life of vemurafenib, the full inhibitory effect of vemurafenib on a concomitant medicinal product medication might not be observed before 8 days of vemurafenib treatment.

After cessation of vemurafenib treatment, a washout of 8 days might be necessary to avoid an interaction with a subsequent treatment.

Effects of vemurafenib on substance transport systems

In vitro studies have demonstrated that vemurafenib is an inhibitor of the efflux transporter (P-gp). The clinical relevance of this finding is unknown. It cannot be excluded that vemurafenib may increase the exposure of other medicines transported by P-gp.

The possible effect of vemurafenib on other transporters (e.g. BCRP) is currently unknown.

Effects of concomitant medicines on vemurafenib

In vitro studies suggest that CYP3A4 metabolism and glucuronidation are responsible for the metabolism of vemurafenib. Biliary excretion appears to be another important elimination pathway. There are no clinical data available showing the effect of strong inducers or inhibitors of CYP3A4 and/or

transport protein activity on vemurafenib exposure. Vemurafenib should be used with caution in combination with potent inhibitors of CYP3A4, glucuronidation and/or transport proteins (e.g. ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, nefazodone, atazanavir).

Concomitant administration of potent inducers of P-gp, glucuronidation, and/or CYP3A4 (e.g. rifampicin, rifabutin, carbamazepine, phenytoin or St John's Wort [hypericum perforatum]) may lead to supoptimal exposure to vemurafenib and should be avoided. The CHMP requested the applicant to perform an interaction study with rifampicin and ketoconazole. This is currently adequately addressed in the SmPC. This post-authorisation measure is covered in the RMP.

In vitro studies have demonstrated that vemurafenib is a substrate of the efflux transporter, P-gp. The effects of P-gp inducers and inhibitors on vemurafenib exposure are unknown. It cannot be excluded that vemurafenib pharmacokinetics could be affected by medicines that inhibit or influence P-gp (e.g. verapamil, clarithromycin, cyclosporine, ritonavir, quinidine, dronedarone, amiodarone, itraconazole, ranolazine). The CHMP requested the applicant to perform an *in vitro* characterisation study on transport proteins. This is currently adequately addressed in the SmPC. This post-authorisation measure is covered in the RMP.

It is currently unknown whether vemurafenib is a substrate also to other transport proteins.

As elimination is primarily via CYP3A4 and vemurafenib appears to be a Pgp substrate, a combined CYP3A4 and Pgp inhibitor might therefore affect more than 70% of the elimination of vemurafenib. Induction of CYP3A4 by vemurafenib was seen with a mean 32% decrease in AUC of a CYP3A4 substrate and with the largest individual effect of 80% decrease. This may be clinically relevant and further studies have been included in the RMP to address this risk.

2.4.5. Conclusions on clinical pharmacology

The CHMP was of the opinion that the clinical pharmacology studies submitted by the applicant were adequate. There is some missing information on drug-drug interactions, the degree of CYP3A4 metabolism and the effects of CYP3A4 inhibitors and inducers on vemurafenib exposure. However, these issues have been adequately addressed in the SmPC with proper warnings and precautions of use and, in addition, the CHMP has requested the applicant to perform several studies to provide the missing information. There was missing information on the importance of hepatic and renal clearance. However, this was considered acceptable since it has been adequately covered in the SmPC and the RMP. The CHMP considered that the benefit risk balance was not affected by this missing information.

There was uncertainty on the absolute bioavailability which hindered the interpretation of the mass balance study. The CHMP has recommended that the applicant perform an absolute bioavailability study.

2.5. Clinical efficacy

2.5.1. Dose response study

Selection of the Phase III dose was based on nonclinical data and clinical efficacy and safety observed in the Phase 1 study, PLX06-02.

The goal of the Phase 1 study was to use the highest dose of vemurafenib that could be tolerated in order to maximize the therapeutic index for metastatic melanoma. The dose escalation phase of PLX06-02 was based on a modified 3+3 accelerated-titration design. Briefly, 3-4 patients per dose were to be treated for 4 weeks, with dose increases of 50%-100% in the absence of dose limiting

toxicities. Up to 6 patients were to be treated if one dose-limiting toxicity (DLT) was observed at a given dose, and a dose was considered to be higher than the maximum tolerated dose if 2 or more DLTs were observed in the cohort of 6 patients. The dose range of 160 mg bid to 1120 mg bid was evaluated with the optimized MBP formulations.

DLTs, primarily Grade 3 rash and Grade 3 fatigue, were observed in 4 patients at 1120 mg bid. Therefore, the maximum tolerated dose of 960 mg bid, representing the approximate midpoint between 720 mg bid and 1120 mg bid, was selected for further clinical development.

2.5.2. Main study

NO25026 (BRIM 3): A Randomized, Open-label, Controlled, Multicenter, Phase III Study in Previously Untreated Patients With Unresectable Stage IIIC or Stage IV Melanoma with V600E BRAF Mutation Receiving vemurafenib or Dacarbazine.

Methods

Inclusion criteria

Patients had to meet all of the following criteria to be included in the study:

1. Male or female patients ≥ 18 years of age

2. Histologically confirmed metastatic melanoma (surgically incurable and unresectable Stage IIIC or Stage IV (American Joint Committee on Cancer [AJCC]). Unresectable Stage IIIC disease needed confirmation from a surgical oncologist.

3. Treatment-naïve, i.e., no prior systemic anti-cancer therapy for advanced disease (Stage IIIC and IV). Only prior adjuvant immunotherapy was allowed.

4. Must have had a BRAFV600E-positive mutation (by Roche cobas test) prior to administration of study treatment

5. ECOG performance status of 0 or 1

6. Life expectancy > 3 months

7. Measurable disease by RECIST criteria (version 1.1) prior to the administration of study treatment

8. Must have recovered from effects of any major surgery or significant traumatic injury at least 14 days before the first dose of study treatment

9. Cutaneous SCC lesions identified at baseline must be excised. Adequate wound healing was required prior to study entry. Baseline skin exam was required for all patients.

10. Adequate haematologic, renal, and liver function as defined by laboratory values performed within 28 days prior to initiation of dosing:

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
- Platelet count ≥ 100 x 10^9/L
- Haemoglobin ≥ 9 g/dL
- Serum creatinine ≤ 1.5 x upper limit of normal (ULN)
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN
- Bilirubin ≤ 1.5 x ULN (for patients with Gilbert's Syndrome, bilirubin ≤ 3 x ULN)

- Alkaline phosphatase ≤ 2.5 x ULN (≤ 5 x ULN for patients with concurrent liver metastases)

11. For premenopausal women, negative serum pregnancy test within 10 days prior to commencement of dosing; women of non-childbearing potential were included if they were either surgically sterile or postmenopausal for ≥ 1 year

12. For fertile men and women, the use of an effective method of contraception during treatment and for at least 6 months after completion of treatment as directed by their physician, in accordance with local requirements

13. Absence of any psychological, familial, sociological or geographical condition that would potentially hamper compliance with the study protocol and follow-up schedule; such conditions were discussed with the patient before trial entry

14. A signed informed consent form (ICF) obtained prior to study entry and prior to performing any study-related procedures

Exclusion criteria

Patients meeting any of the following criteria were excluded from the study:

1. Any active central nervous system (CNS) lesion (i.e., those with radiographically unstable, symptomatic lesions). However, patients treated with stereotactic therapy or surgeries were eligible if patient remained without evidence of disease progression in brain ≥ 3 months. Patients were also required to be off corticosteroid therapy for ≥ 3 weeks. Whole brain radiotherapy was not allowed with the exception of patients who had definitive resection or stereotactic therapy of all radiologically detectable parenchymal lesions

2. History of carcinomatous meningitis

3. Regional limb infusion or perfusion therapy

4. Anticipated or ongoing administration of anti-cancer therapies other than those administered in this study

5. Pregnant or lactating women

6. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant small bowel resection that would preclude adequate vemurafenib absorption (patients had to be able to swallow pills)

7. Mean QTc interval ≥ 450 msec at screening

8. National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI CTCAE) Version 4.0 grade 3 haemorrhage within 4 weeks of starting the study treatment

9. Any of the following within the 6 months prior to study drug administration:

myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, serious cardiac arrhythmia requiring medication, uncontrolled hypertension, cerebrovascular accident or transient ischemic attack, or symptomatic pulmonary embolism

10. Known clinically significant active infection

11. History of allogeneic bone marrow transplantation or organ transplantation

12. Other severe, acute or chronic medical or psychiatric condition or laboratory abnormality that could increase the risk associated with study participation or study drug administration, or could interfere

with the interpretation of study results, which in the judgment of the investigator would make the patient inappropriate for entry into this study

13. Previous malignancy within the past 5 years, except for basal or squamous cell carcinoma of the skin, melanoma in-situ, and carcinoma in-situ of the cervix (an isolated elevation in prostate-specific antigen in the absence of radiographic evidence of metastatic prostate cancer was allowed)

14. Previous treatment with a BRAF inhibitor

15. Known human immunodeficiency virus (HIV) positivity, AIDS-related illness, active hepatitis B virus, or active hepatitis C virus

16. Randomization to this trial at another participating site

Study Participants

A total of 680 patients were planned to be enrolled at centers in Western Europe, North America, Australia/New Zealand, and Israel. Patients were randomly assigned to treatment in a 1:1 randomization ratio to one of two treatment arms.

Treatments

Patients were to receive continuous oral doses of vemurafenib 960 mg bid without scheduled dose interruption. Patients took four 240 mg tablets in the morning and four 240 mg tablets in the evening (960 mg bid for a total daily dose of 1920 mg). After 8 hours of fasting on pharmacokinetic collection days (Day 1 of Cycles 1-4, 6, 8, and 10 and Day 1 of all subsequent cycles), vemurafenib was administered to patients as part of the scheduled study visit in the clinic; patients then had 4 hours of post-dose fasting. If patients were unable to tolerate post-dose fasting on the morning of pharmacokinetic collection days, patients could have a light snack (i.e., crackers, toast, juice, and water) if needed. On days when dosing was administered at home, patients were not required to take their study treatment under fasting conditions.

Dacarbazine was administered intravenously 1000 mg/m^2 up to 60 minutes on Day 1 of every 3 weeks (3 weeks was one cycle length). Dosing could be given up to 2 days early or 7 days late. No fasting as required for patients taking dacarbazine and pharmacokinetic samples were not obtained for these patients during the study.

Patients were treated until the development of progressive disease, unacceptable toxicity, and/or consent withdrawal.

The following medications and treatments were not allowed during the study treatment period:

- Other anti-cancer therapies
- Radiotherapy for the treatment of disease, with the exception of limited field radiotherapy for palliative bone pain because of a pre-existing bone metastasis (if it was not considered a target lesion for RECIST assessments)

Objectives

The primary objective of this study was to evaluate the efficacy of vemurafenib as a monotherapy compared to dacarbazine in terms of progression-free survival (PFS) and overall survival (OS) in previously untreated patients with BRAFV600E mutation-positive metastatic melanoma.

The secondary objectives were as follows:

• To further assess the efficacy of vemurafenib compared to dacarbazine based on best overall response rate (BORR), time to response, and duration of response

• To evaluate the tolerability and safety profile of vemurafenib using the NCI CTCAE (version 4.0)

• To further characterize the pharmacokinetic (PK) profile of vemurafenib

• To contribute to the validation of the cobas 4800 BRAF V600 Mutation Test as a companion diagnostic test for the detection of BRAFV600 mutations in DNA extracted from formalin-fixed paraffin-embedded tumour (FFPET) samples

Outcomes/endpoints

There were two co-primary efficacy endpoints for this study: OS and PFS.

The secondary efficacy endpoints were BORR (RECIST v1.1), duration of response and time to response.

Tumour assessments were done at screening, every 6 weeks for the first 12 weeks, every 9 weeks subsequently, and at the final visit. Patients were followed for AEs (with exception of SCC) up to 28 days after the last dose in all patients. All SCC events occurring at any time during the study or follow-up period (every 3 months until patient death, withdrawal of consent, or lost to follow-up) were collected and reported as a serious adverse event (SAE) to the sponsor.

OS was defined as the time from randomization to death from any cause. For patients who were alive at the time of analysis data cut-off, OS time was censored at the last date the patient was known to be alive prior to the clinical cut-off date. The last date the patient was known to be alive was derived as the latest date of contact or study assessment.

The final analysis for PFS was performed at the time of the interim efficacy analysis for OS. PFS was defined as the time from randomization to the date of disease progression (based on tumour assessment date) or death from any cause, whichever occurred first. The death of a patient without a reported progression was considered as an event on the date of death. Patients who had neither progressed nor died were censored on the date of last evaluable tumour assessment prior to the clinical cut-off date. PFS for patients who had no post-baseline assessment and who did not have an event were censored on the date of randomization. There was no blinded independent central review of PFS.

Duration of response was evaluated for patients who satisfied the criteria for BORR (confirmed).

Sample size

Approximately 680 patients were planned to be randomized (1:1) to receive either vemurafenib (Arm A) or dacarbazine (DTIC) (Arm B).

For OS, a total of 196 deaths (100% information), at an accrual of 41 patients per month, provided 80% power to detect a hazard ratio of 0.65 for death for vemurafenib treatment relative to dacarbazine treatment, under the following assumptions: 0.045 significance level (two-sided), median survival of 8 months in the dacarbazine arm and 12.3 months in the vemurafenib arm.

Randomisation

Randomization was performed using an interactive voice recognition system (IVRS). Following the screening period (of up to 28 days), eligible patients were randomized to receive either:

- Experimental Arm A: oral vemurafenib administered bid at a dose of 960 mg
- Control Arm B: dacarbazine administered intravenously 1000 mg/m^2 on Day 1 every 3 weeks (3 week cycle)

The treatment allocation was based on a minimization algorithm using the following balancing factors:

- Geographic region (North America, Western Europe, Australia/New Zealand, others)
- Eastern Cooperative Oncology Group (ECOG) performance status (0 vs.1)
- Metastatic classification (unresectable Stage IIIC, M1a, M1b, and M1c)
- Serum lactate dehydrogenase (LDH) normal vs. LDH elevated

Blinding (masking)

This study was designed as an open-label trial.

Statistical methods

The type 1 error (alpha) for this study was 0.05 (two-sided). To maintain the alpha level of 0.05 (two-sided) while accounting for two co-primary endpoints, statistical significance for the comparison of OS was based on an alpha level of 0.045 (two-sided), and statistical significance for the comparison of PFS was based on an alpha level of 0.005 (two-sided).

The Log-rank test was used for analysis of both OS and PFS.

Survival time for patients with no post-baseline survival information was censored on the date of randomization. The primary analysis of OS was a comparison of the two treatment groups using an unstratified log-rank test (two-sided).

For PFS, a total of 187 PFS events (disease progression or death) provided 90% power to detect a hazard ratio of 0.55 for vemurafenib treatment relative to dacarbazine treatment, under the following assumptions: 0.005 significance level (two-sided), median PFS of 2.5 months in the dacarbazine arm and 4.5 months in the vemurafenib arm. The primary analysis of PFS was a comparison of the two treatment groups using an unstratified log-rank test (two-sided).

A total of 196 deaths (100% information) provided 80% power to detect a hazard ratio of 0.65 for death for vemurafenib treatment relative to dacarbazine treatment, under the assumption of a median survival of 8 months in the dacarbazine arm and 12.3 months in the vemurafenib arm

One interim analysis for the co-primary endpoint of OS was planned at 50% information. The final analysis of the co-primary endpoint of PFS was planned to occur at the time of the interim analysis of OS. Review of the interim analysis results was performed by an external Data Safety Monitoring Board (DSMB).

There was no planned interim analysis for PFS.

The primary analyses of OS and PFS was performed for the PP population. The PP population was defined as treated patients, excluding patients who violated any of the following inclusion criteria:

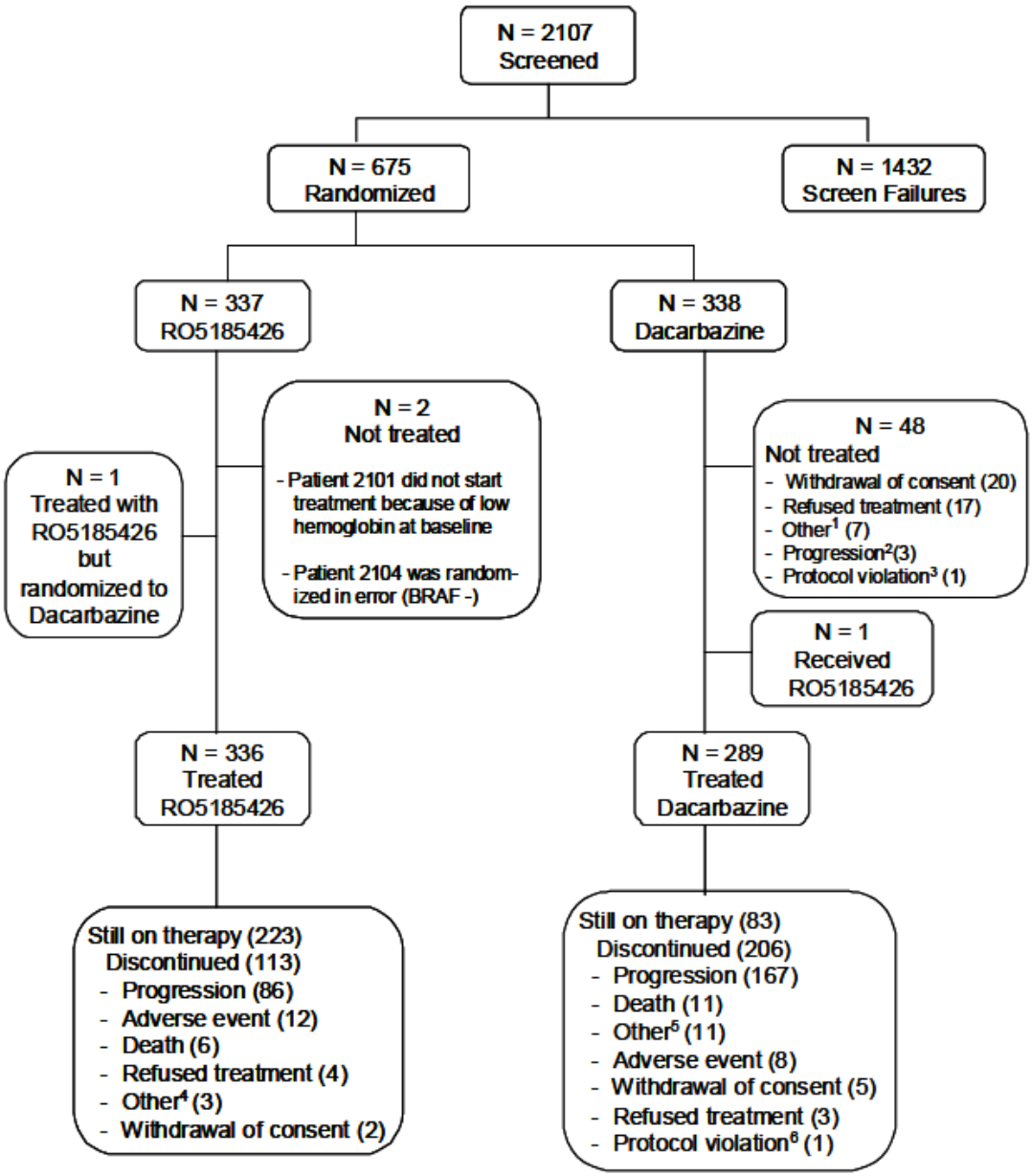
- Histologically confirmed metastatic melanoma (surgically incurable and unresectable Stage IIIC or Stage IV, AJCC)
- Positive for BRAFV600 mutation by the cobas 4800 BRAF V600 Mutation Test
- No prior systemic anti-cancer therapy for this disease
- ECOG performance status 0 or 1.

The ITT population was defined as all randomized patients, whether or not study treatment was received. The ITT population was analyzed according to the treatment assigned at randomization.

Results

Participant flow

Figure 9 Patient disposition as of 30th December 2010



Recruitment

A total of 104 centres randomized patients into this study. Enrolment by centre ranged from 1 to 30 patients across centres in the U.S., Canada, United Kingdom, France, Italy, Germany, Netherlands, Sweden, Switzerland, Israel, Australia, and New Zealand. Among randomized patients, a total of 408 (60%) patients were enrolled in centres in Western Europe, 172 (25%) in North America, 77 (11%) in Australia/New Zealand, and 18 (3%) in Israel.

Conduct of the study

Study enrolment was initiated in January 2010 and completed in December 2010. There was a change in the statistical assumptions and PFS was changed from a secondary endpoint to a co-primary endpoint; as a result, the planned interim analysis was projected to occur sooner than originally planned. The SAP was revised prior to the interim analysis of OS to reflect the changes in the protocol.

The planned interim analysis of OS occurred on January 14, 2011. The DSMB recommended the cross over of patients treated with dacarbazine to vemurafenib.

A total of 14 (4.2%) patients randomized to the vemurafenib group and 23 (6.8%) patients randomized to the dacarbazine group had a major protocol deviation.

Major protocol deviations are presented in Table 18.

Table 18 Major Protocol deviations (ITT population) – Study NO25026

	Dacarbazine (N=338)	Vemurafenib (N=337)
Patients with any major protocol deviation	23 (6.8%)	14 (4.2%)
Patients with eligibility deviation	7 (2.1%)	8 (2.4%)
Tumour tissue not positive at entry for V600 mutation by cobas 4800 test	1 (0.3%)	1 (0.3%)
Received prohibited prior systemic anti-cancer therapy for this disease	1 (0.3%)	3 (0.9%)
No measurable disease	5 (1.5%)	5 (1.5%)
Patients with on-study deviation	17 (5.0%)	7 (2.1%)
Received incorrect study treatment	1(0.3%)	0(0.0%)
Received non-protocol anti-cancer therapy without disease progression	16 (4.7%)	7 (2.1%)

Baseline data

A summary of the baseline demographics of the study population is shown in Table 19.

Table 19 Summary of Demographics (ITT Population) – Study NO25026

	Dacarbazine N = 338	Vemurafenib N = 337
Sex (num,%) FEMALE MALE n	 157 (46%) 181 (54%) 338	 137 (41%) 200 (59%) 337
Race (num,%) WHITE HISPANIC OTHER * n	 338 (100%) - - 338	 333 (99%) 2 (<1%) 2 (<1%) 337
Age in years Mean SD SEM Median Min-Max n	 52.6 13.89 0.76 52.5 17 - 86 338	 55.2 13.80 0.75 56.0 21-86 337

Age in years <65yrs >=65yrs n	 270 (80%) 68 (20%) 68 (20%) 338	 244 (72%) 93 (28%) 93 (28%) 337
Age in years <=40yrs 41-54yrs 55-64yrs 65-74yrs >=75yrs n	 70 (21%) 114 (34%) 86 (25%) 46 (14%) 22 (7%) 338	 48 (14%) 111 (33%) 85 (25%) 65 (19%) 28 (8%) 337
Weight in kg Mean SD SEM Median Min-Max n	 78.44 17.678 0.966 77.10 35.0 - 143.5 335	 79.15 18.098 0.992 78.60 37.0 – 151.4 333

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
* "Other" race was recorded by the investigator as Syrian in 1 patient and non-Hispanic in 1 patient.

A summary of the stratification factors is shown in Table 20.

Table 20 Summary of Stratification Factors Provided by Investigators to IVRS by Randomization Arm (ITT Population) – Study NO25026

	Dacarbazine	**vemurafenib**
	N = 338	**N = 337**
Geographic Region		
Australia/New	38 (11%)	39 (12%)
Zealand		
North America	86 (25%)	86 (26%)
Others	11 (3%)	7 (2%)
Western Europe	203 (60%)	205 (61%)
n	338	337
ECOG Performance Status		
0	230 (68%)	229 (68%)
1	108 (32%)	108 (32%)
n	338	337
Metastatic Classification		
Unresectable Stage	13 (4%)	20 (6%)
IIIC		
M1a	40 (12%)	34 (10%)
M1b	65 (19%)	62 (18%)
M1C	220 (65%)	221 (66%)
n	338	337

Serum Lactate Dehydrogenase		
LDH Elevated	142 (42%)	142 (42%)
LDH Normal	196 (58%)	195 (58%)
n	338	337

Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
n represents number of patients contributing to summary statistics.

A summary of baseline disease characteristics is shown in Table 21.

Table 21 Summary of Disease Characteristics (ITT Population) – Study NO25026

	Dacarbazine N = 338	**Vemurafenib N = 337**
Number of Metastatic Sites at Baseline		
Mean	2.6	2.6
SD	1.33	1.37
SEM	0.07	0.08
Median	2.0	2.0
Min-Max	1 - 8	1 - 8
n	330	330
Number of Metastatic Sites at Baseline		
<3	181 (55%)	185 (56%)
>=3	149 (45%)	145 (44%)
n	330	330
Sum of Diameter of Target Lesion at Baseline		
Mean	79.2	88.2
SD	57.29	96.50
SEM	3.14	5.30
Median	66.0	66.5
Min-Max	9 - 295	9 - 1310
n	333	332
Time Since Metastatic Diagnosis(months)		
Mean	9.1	8.8
SD	18.95	15.28
SEM	1.09	0.90
Median	3.0	3.0
Min-Max	0 - 184	0 - 109
n	300	288
Time Since Metastatic Diagnosis (months)		
<6	216 (72%)	191 (66%)
>=6	84 (28%)	97 (34%)
n	300	288
Brain Metastasis		
NO	332 (99%)	333 (100%)
YES	2 (<1%)	-
n	334	333
Histological Subtypes		
ACRAL LENTIGINOUS	3 (<1%)	1 (<1%)
LENTIGO MALIGNA	5 (1%)	1 (<1%)
NODULAR	78 (23%)	78 (23%)
OTHER	143 (42%)	153 (45%)

SUPERFICIAL SPREADIN	109 (32%)	104 (31%)
n	338	337

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.

Sanger sequencing results were available for a total of 220 randomized patients (111 vemurafenib, 109 dacarbazine patients). Among the 220 patients were 2 patients whose tumours were mutation-negative by the cobas test at screening (Table 22).

Table 22 Summary of Mutation Status (ITT Population) – Study NO25026

	Dacarbazine N = 338	**Vemurafenib N = 337**
BRAF mutation status by Sanger		
Non-V600E	33 (30%)	23 (21%)
V600E	76 (70%)	88 (79%)
n	109	111
Non-V600E BRAF mutation by Sanger		
No Sequence	17 (52%)	10 (43%)
Other	1 (3%)	-
V600E2	-	1 (4%)
V600K	9 (27%)	10 (43%)
WT	6 (18%)	2 (9%)
n	33	23

Percentages are based on n (number of valid values). Percentages not calculated if n < 10.

Numbers analysed

A summary of the analysis population is shown in Table 23.

Table 23 Analysis population (ITT population) – Study NO25026

	DTIC	RO5185426
Randomized Patients	338	337
Evaluable for Overall Survival at Interim Analysis (a)	336(99.41%)	336(99.70%)
Evaluable for Progression-Free Survival Analysis (b)	274(81.07%)	275(81.60%)
Evaluable for Best Overall Response (confirmed) Analysis (c)	220(65.09%)	219(64.99%)

(a) Randomized on or before December 15, 2010
(b) Randomized on or before October 27, 2010
(c) Randomized on or before September 22, 2010
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$PROD/cdpt7204/i25026b/reports/t_sumpopn_.out 16MAR2011 1:42 Page 1 of 1

Outcomes and estimation

Primary endpoints

Overall Survival

A summary of the updated OS data with data cut-off at 03 October 2011 is shown in Table 24 and Figure 10.

Table 24 Overall Survival – Study NO25026

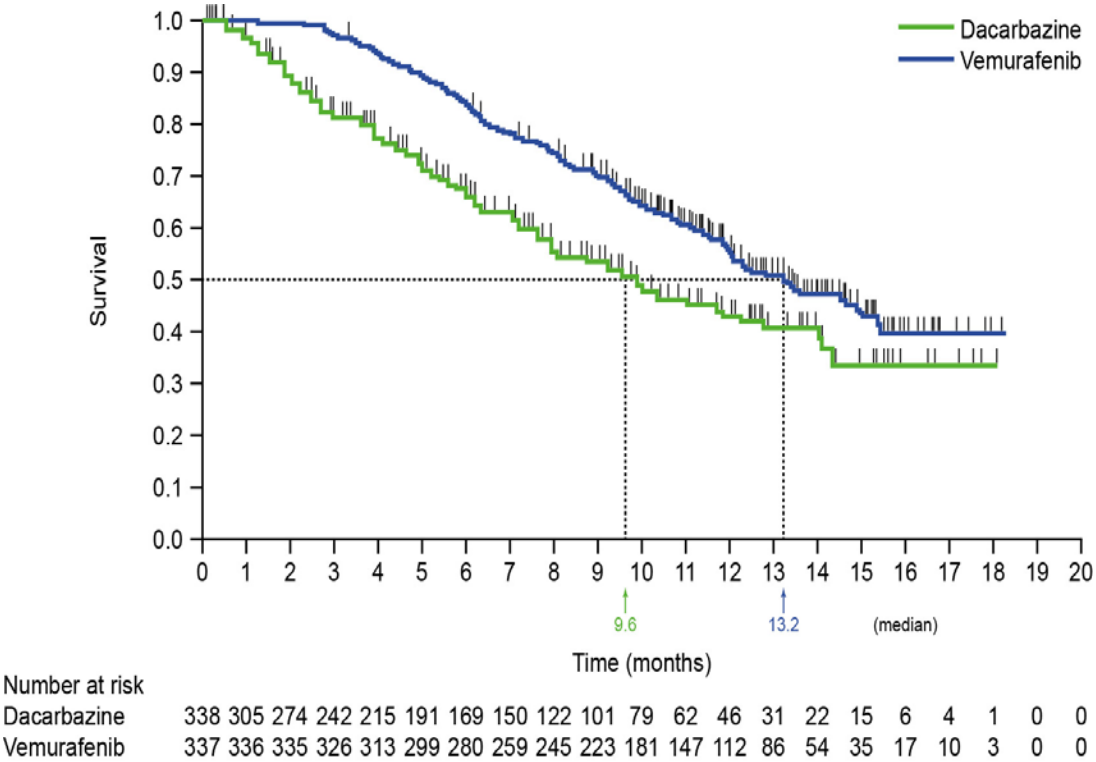
		With Censoring at Date of Crossover [a]		Without Censoring at Date of Crossover [b]	
		Dacarbazine (N=338)	**Vemurafenib (N=337)**	**Dacarbazine (N=338)**	**Vemurafenib (N=337)**
Overall survival	Number of Deaths by arm	152	159	175	159
	Total Number of Deaths	311		334	
	Median (KM) (months) (95% CI)	9.6 (7.9, 11.8)	13.2 (12.0, 15.0)	9.9 (9.1, 12.2)	13.2 (12.0, 15.0)
	6-month survival rate (KM) (95% CI)	66% (61%, 72%)	84% (80%, 88%)	67% (62%, 73%)	84% (80%, 88%)
	12-month survival rate (KM) (95% CI)	43% (36%, 49%)	55% (49%, 61%)	44% (38%, 50%)	55% (49%, 61%)
	Hazard ratio (95% CI)	0.62 (0.49, 0.77)		0.67 (0.54, 0.84)	
	p-value (log rank test)	p<0.0001		p=0.0003	

KM = Kaplan-Meier estimate.

[a] For dacarbazine patients who crossed over to receive vemurafenib after the DSMB recommendation in January 2011, all survival data up to the time of crossover are included in the analysis and the patient is analyzed as alive as of the date of crossover (survival time was censored at the date of crossover).

[b] No censoring at the date of crossover was performed for dacarbazine patients who crossed over to receive vemurafenib.

Figure 10 **Kaplan-Meier plot of duration of survival (data cut-off 03/10/11)– Study NO25026**



A summary of the OS data submitted at different data cut-off dates. The results show an increase in hazard ratio from 0.37 to 0.62 with progressively mature data. It is of note that the number of cross-over patients from dacarbazine to vemurafenib was still low at the last data cut-off.

Table 25 **Overall survival in previously untreated patients with BRAF V600 mutation positive melanoma by study cut-off date (N=338 dacarbazine, N=337 vemurafenib) – Study NO25026**

Cut-off dates	Treatment	Number of deaths (%)	Hazard Ratio (95% CI)	Number of cross-over patients (%)
December 30, 2010	dacarbazine	75 (22)	0.37 (0.26, 0.55)	0 (not applicable)
	vemurafenib	43 (13)		
March 31, 2011	dacarbazine	122 (36)	0.44 (0.33, 0.59) [f]	50 (15%)
	vemurafenib	78 (23)		
October 3, 2011	dacarbazine	175 (52)	0.62 (0.49, 0.77) [f]	81 (24%)
	vemurafenib	159 (47)		

[f] Censored results at time of cross-over
Non-censored results at time of cross-over: March 31: HR (95% CI) = 0.47 (0.35, 0.62); October 3: HR (95% CI) = 0.67 (0.54, 0.84)

Progression Free Survival

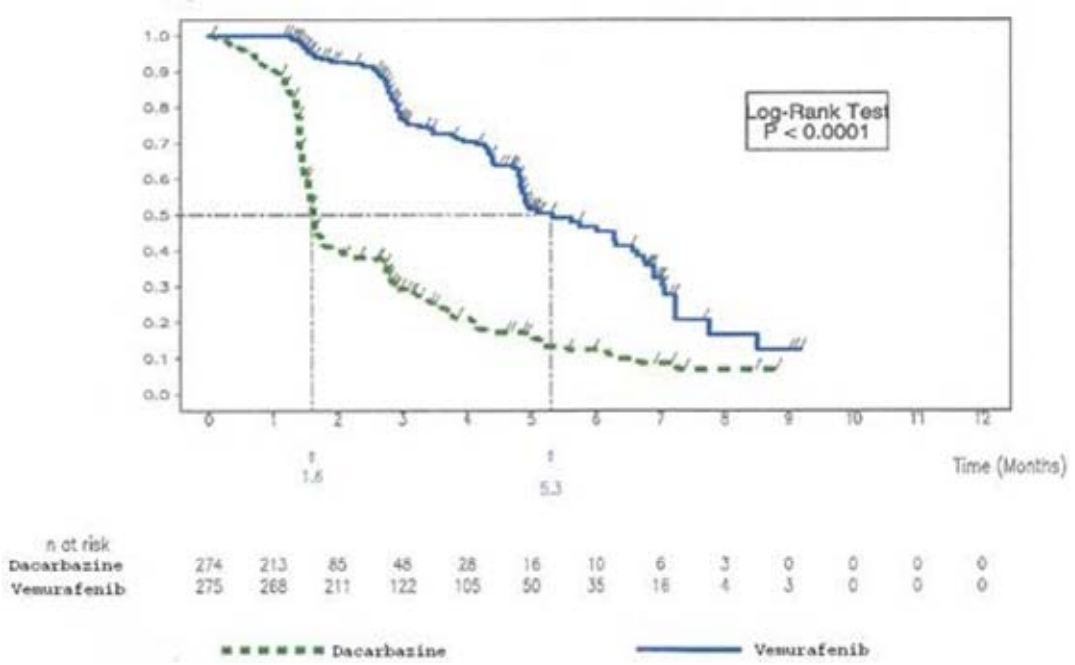
Table 26 summarizes the results of the analysis of the co-primary endpoint of PFS as of the clinical cut-off date 30/12/11. Among the 549 ITT patients evaluable for analysis of PFS, a total of 286 patients had experienced disease progression or had died: 104 in the vemurafenib group and 182 in the dacarbazine group.

Table 26 Analysis of Progression-Free Survival – Study NO25026

	Dacarbazine (N=274)		Vemurafenib (N=275)
Patients included in analysis	274 (100.0 %)		275 (100.0 %)
Patients with event	182 (66.4 %)		104 (37.8 %)
Patients without events	92 (33.6 %)		171 (62.2 %)
Time to event (months)			
Median[a]	1.61		5.32
95% CI for Median[b]	[1.58;1.74]		[4.86;6.57]
25% and 75%-Quartile	1.41;3.48		3.25;7.23
Range[c]	0.03 to 8.80		0.03 to 9.17
p-Value (Log-Rank Test)		<.0001	
Hazard Ratio (unstratified)		0.26	
95% CI		[0.20;0.33]	
Six month duration			
Patients remaining at risk[d]	10		35
Event Free Rate[e]	0.12		0.47
95% CI for Rate[f]	[0.07;0.18]		[0.38;0.55]

a. Kaplan-Meier estimate
b. 95% CI for median using the method of Brookmeyer and Crowley
c. Includes censored observations
d. Number of patients in the respective treatment arm who have not had an event up to the end of six months, nor have been censored
e. Kaplan-Meier estimate of the event free rate at six months
f. Standard error is estimated using Greenwood's formula

Figure 10 Kaplan-Meier plot of duration of progression free survival (data cut-off 30/12/10) – Study NO25026



Secondary endpoints

Best Overall Response

A total of 106 of 219 patients in the vemurafenib group and 12 of 220 patients in the dacarbazine group had a response that was confirmed. The response rate in the vemurafenib group was 48.4% (95% CI: 41.6% – 55.2%) and in the dacarbazine group was 5.5% (95% CI: 2.8%, 9.3%) (p<0.0001, Chi-squared test with Shouten correction).

The difference in ORR was 42.95% (95% CI: 35.4% – 50.5%) in favour of vemurafenib treatment.

Duration of Response

The Kaplan-Meier estimate of the median duration of response was 5.49 months in the vemurafenib group (95% CI: 3.98 – 5.72) and was not reached in the dacarbazine group (95% CI: 4.60, not reached). At the time of analysis, the duration of response ranged from 1.22 to 7.62 months in the vemurafenib group and 1.18 to 5.55 months in the dacarbazine group.

The majority of responders (75%) responded to treatment with vemurafenib by the time of the first post baseline tumour assessment (1.6 months). Among the 12 dacarbazine patients with a confirmed response, the median time to response was 2.72 months (range: 1.6 to 5.8).

Ancillary analyses

The subgroup analyses for OS and PFS are presented in Figure 11 and 12 at the cut-off data of 30/12/10.

Subgroup analyses

Figure 11 Forest Plot for Overall Survival by Subgroup – Study NO25026

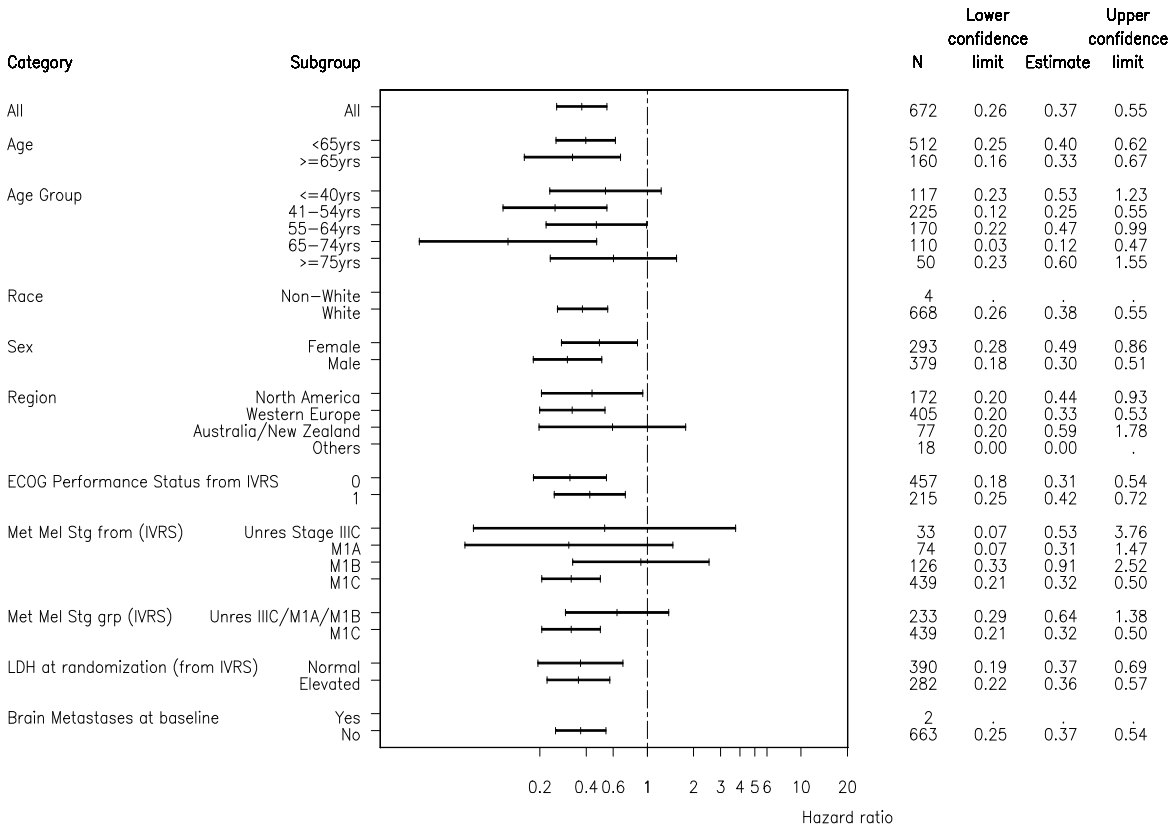
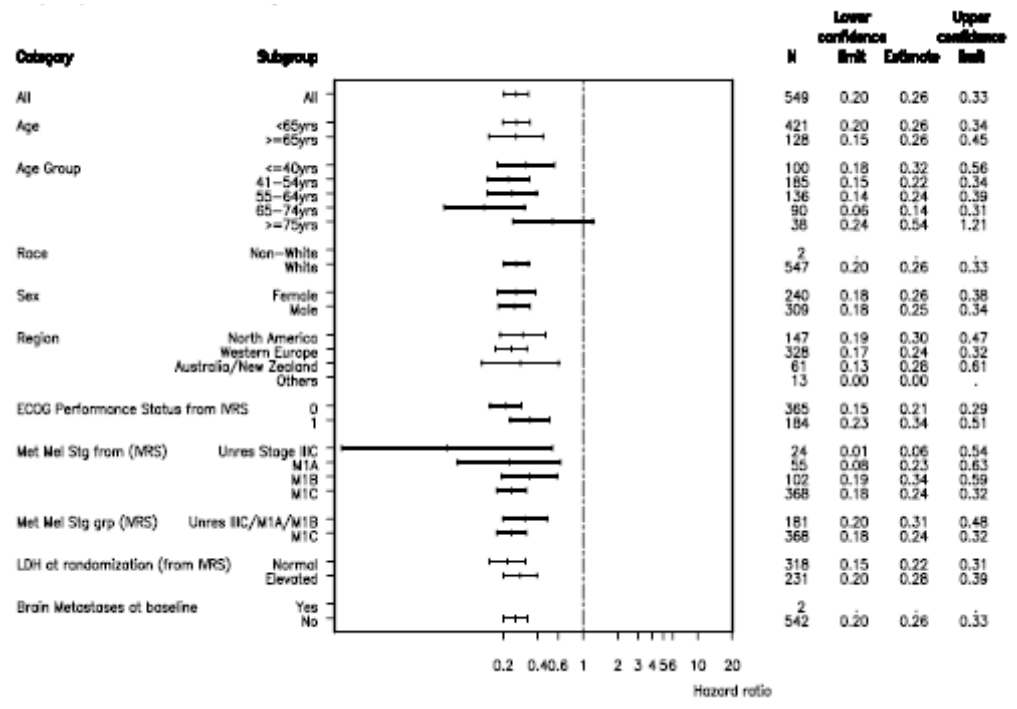


Figure 12 Forest Plot for progression free survival by Subgroup – Study NO25026



Quality of life

Analyses of FACT-M and its subscales suggested that there was no evidence that quality of life measured over time on study treatment differed between treatment groups.

Analyses of pain score reported by the patient using a visual analog scale suggested that there was no evidence that pain score measured over time on study treatment differed between treatment groups.

Analyses of the proportions of patients who experienced improvement from baseline as measured by oxygen saturation, use of narcotic pain analgesics, and physician's assessment of global performance status suggested that there was no difference between the treatment groups.

Mutation Analyses

Figure 13 summarizes OS results by BRAF V600 mutation status as determined by Sanger sequencing. Treatment benefit of vemurafenib treatment on OS was observed for patients in the subgroup in whose tumours the V600E mutation was detected by both the cobas 4800 BRAF V600 Mutation Test and Sanger sequencing (N=164) (HR 0.58; 95% CI: 0.33 – 1.02) and the subgroup in whose tumours the V600E mutation was not detected by Sanger sequencing but whose tumours carry activating BRAF V600 mutations detected by the cobas test (N=56) (HR 0.44; 95% CI: 0.17 – 1.15).

Figure 13 Forest Plot for Hazard ratios and 95% confidence intervals for OS by mutation status – Study NO25026

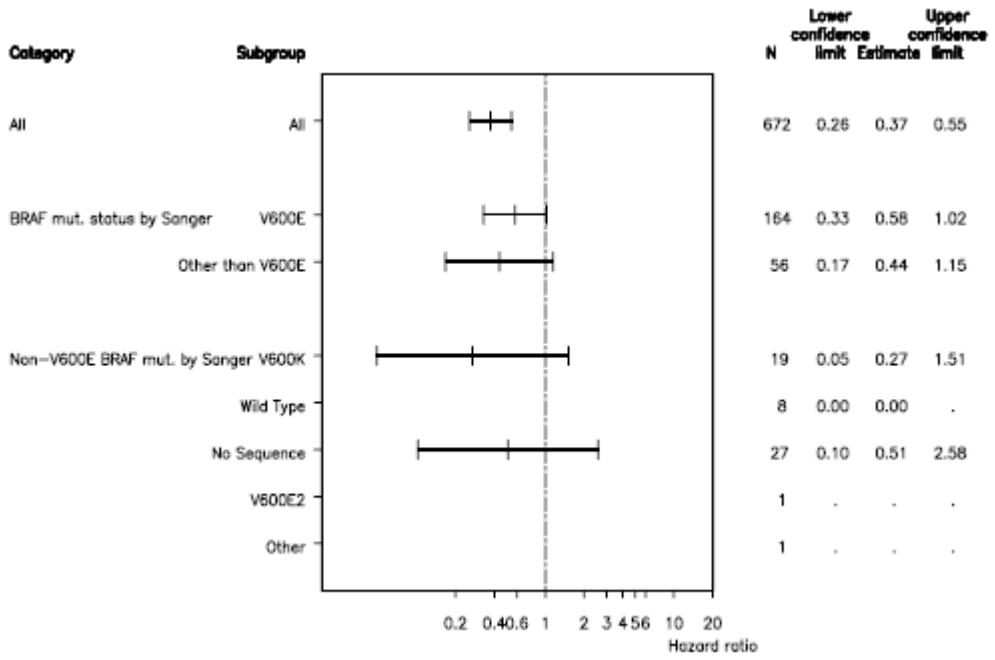
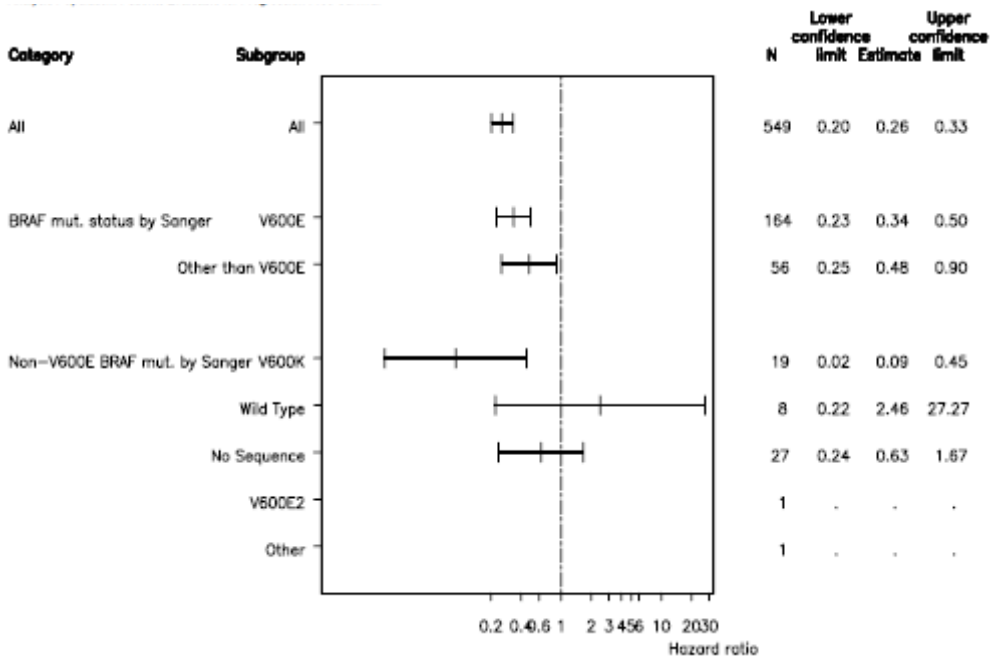


Figure 14 summarizes PFS results by BRAF V600 mutation status as determined by Sanger sequencing. Treatment benefit of vemurafenib treatment on PFS was observed for patients in the subgroup in whose tumours the V600E mutation was detected by both the cobas test and Sanger sequencing (N=164) (HR 0.34; 95% CI: 0.23, 0.50) and the subgroup in whose tumours the V600E mutation was not detected by Sanger sequencing but whose tumours carry activating BRAF V600 mutations detected by the cobas test (N=56) (HR 0.48; 95% CI: 0.25, 0.90).

Figure 14 Forest Plot for Hazard ratios and 95% confidence intervals for progression free survival by mutation status – Study NO25026



LDH and tumour stage

The OS results with respect to lactate dehydrogenase (LDH) and tumours stage at presented in Table 27.

Table 27 Overall survival in previously untreated patients with BRAF V600 mutation positive melanoma by LDH, tumour stage and ECOG status (October 3, 2011 cut-off, uncensored and censored results at time of cross over) – Study NO25026

Uncensored data			
Stratification variable	N	Hazard Ratio	95% Confidence Interval
LDH normal	391	0.72	0.52; 1.00
LDH >ULN	284	0.52	0.43; 0.76
Stage IIIc/M1A/M1B	234	0.94	0.62; 1.42
Stage MIC	441	0.57	0.45; 0.74
ECOG PS=0	459	0.69	0.52; 0.92
ECOG PS=1	216	0.62	0.45; 0.86
Censored data			
Stratification variable	N	Hazard Ratio	95% Confidence Interval
LDH normal	391	0. 65	0.46; 0.91
LDH >ULN	284	0. 50	0.37; 0.67
Stage IIIc/M1A/M1B	234	0. 87	0.56; 1.34
Stage MIC	441	0. 52	0.40; 0.67
ECOG PS=0	459	0. 64	0.47; 0.86
ECOG PS=1	216	0. 52	0.37; 0.73

Summary of main study

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

Table 28 Summary of Efficacy for trial NO25026 (BRIM-3)

Title: NO25026				
Design	Randomised, active control, open label			
	Duration of main phase:		Study Ongoing. January 4, 2010 (first patient randomized) December 30, 2010 (clinical cut-off date for the CSR)	
	Duration of Run-in phase:		Not applicable	
	Duration of Extension phase:		Ongoing	
Hypothesis	Superiority			
Treatments groups	Test		Vemurafenib: 960 mg bid until disease progression or unacceptable toxicity/intolerability n=336	
	Reference		Dacarbazine (DTIC): intravenously 1000 mg/m2 up to 60 minutes on Day 1 of every 3 weeks until disease progression or unacceptable toxicity/intolerability, n=336	
Endpoints and definitions	Co-Primary endpoints		Overall survival Progression-free survival	
	Secondary endpoints		Best overall response Time to response Duration of response	
Database lock	December 30, 2010			
Results and Analysis				
Analysis description	**Primary Analysis (OS and PFS) and secondary (BORR)**			
Analysis population and time point description	Intent to treat			
Outcome	Treatment group	DTIC	Vemurafenib	Comparative statistics
	Number of subject	336	336	
Data cut-off 03/10/11*	OS	Median 13.2 m	Median 9.9 m	HR: 0.67 P=0.0003
				95% CI 0.54; 0.84
Data cut-off 30/12/10	PFS	Median 1.61 m	Median 5.32	0.26 P< 0.0001
				95% CI 0.20; 0.33

Data cut-off 30/12/10	BORR	12/220 5.5%	106/219 48.4%	95% CI for difference in response rate 35; 51 P< 0.0001

* Please refer to Table 25 for detailed information.

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

Analysis of BORR, PFS and OS was performed across the pivotal NO25026 trial, the NP22657 supportive trial and the PLX06-02 dose finding trial (data not shown).

Clinical studies in special populations

Supportive study

Study NP22657: An Open-Label, Multi-Center, Phase II Study of Continuous Oral Dosing of RO5185426 in Previously treated Patients With Metastatic Melanoma.

Study NP22657 was a single-arm, Multi-Centre, Phase II Study of Continuous Oral Dosing of vemurafenib in Previously Treated Patients with Metastatic Melanoma.

Patients must have had a *BRAF*V600E mutation-positive melanoma (using the Roche cobas 4800 BRAF V600 Mutation Assay) prior to administration of vemurafenib. A summary of the efficacy results is shown in Table 29.

Table 29 Summary of efficacy – Study NP22657

Parameter	**IRC Assessment N=132**	**Investigator Assessment N=132**
BORR [a], confirmed, n (%) [95% CI] [b] CR PR SD	69 (52) [43, 61] 3 (2) 66 (50) 39 (30)	72 (55) [46, 63] 4 (3) 68 (52) 36 (27)
BORR concordance IRC vs Investigator (%)	84	
Duration of response, median mos (KM) [95% CI] [c]	6.5 [5.6, not reached]	5.7 [5.5, 7.1]
PFS, median months (KM) [95% CI] [c]	6.1 [5.5, 6.9]	-
6-month PFS rate (KM) [95% CI]	52% [43, 61]	-
OS, median months [95% CI] [c]	not reached [9.5, not reached]	
6-month OS rate (KM) [95% CI]	77% [70, 85]	

IRC=independent review committee; **BORR**=best overall response rate; **CR**=complete response; **PR**=partial response; **SD**=stable disease; **PFS**=progression-free survival; **OS**=overall survival; **KM**=Kaplan-Meier estimate
[a] RECIST v1.1 criteria
[b] Based on Clopper-Pearson exact method
[c] Median estimated through KM method and CI for median is based on the method of Brookmeyer and Crowley

Of the 132 patients in this study, 56 (42%) had a dose reduction for any reason. Of these 56 patients who had their dose reduced, the majority (39/56 patients) had one dose reduction.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

An open-label, multicenter, international, randomized phase III study supports the use of vemurafenib in previously untreated patients with BRAF V600E mutation-positive unresectable or metastatic melanoma. Patients were randomized to treatment with vemurafenib (960 mg twice daily) or dacarbazine (1000 mg/m2 on day 1 every 3 weeks).

The efficacy of vemurafenib has been evaluated in 336 patients from a phase III clinical trial (NO25026) and 132 patients from a phase II clinical trial (NP 22657). All patients were required to have advanced melanoma with BRAF V600 mutations according to the cobas 4800 BRAF V600 Mutation Test.

The primary endpoint of the pivotal phase III study NO25026 was to assess the efficacy and safety of vemurafenib compared to dacarbazine in melanoma patients with BRAF V600E mutation. The open label, two arm trial design was considered adequate. The inclusion and exclusion criteria were considered acceptable as well as the primary and secondary endpoints. The CHMP had some initial concerns over the premature analysis performed by the applicant, which required modification of the SAP and lead to the DSMB recommendation that patients be allowed to cross over to vemurafenib treatment at the time of the interim analysis. Despite these initial concerns, the applicant provided satisfactory documentation to assess the benefits and risks of vemurafenib treatment and provided sufficient and adequate data to assess and establish the benefit risk balance of the product.

Efficacy data and additional analyses

A total of 675 patients were randomized to vemurafenib (n=337) or dacarbazine (n=338). Most patients were male (56%) and Caucasian (99%), the median age was 54 years (24% were ≥ 65 years), all patients had ECOG performance status of 0 or 1, and the majority of patients had stage M1c disease (65%). The co-primary efficacy endpoints of the study were overall survival (OS) and progression-free survival (PFS).

At the pre-specified interim analysis with a December 30, 2010 data cut-off, significant improvements in the co-primary endpoints of OS ($p<0.0001$) and PFS ($p<0.0001$) (unstratified log-rank test) were observed. Upon Data Safety Monitoring Board (DSMB) recommendation, those results were released in January 2011 and the study was modified to permit dacarbazine patients to cross over to receive vemurafenib. Post-hoc survival analyses were undertaken as described in Table 25. The subgroup analyses supported the data from the primary analyses.

A total of 19 patients out of 220 whose tumours were analysed by retrospective sequencing were reported to have BRAF V600K mutation-positive melanoma in NO25026. Although limited by the low number of patients, efficacy analyses among these patients with V600K-positive tumours suggested treatment benefit of vemurafenib in terms of OS, PFS and confirmed best overall response. No data are available in patients with melanoma harbouring BRAF V600 mutations others than V600E and V600K.

A phase II single-arm, multi-center, multinational study was conducted in 132 patients who had BRAF V600E mutation-positive metastatic melanoma according to the cobas 4800 BRAF V600 Mutation Test and had received at least one prior therapy. The median age was 52 years with 19% of patients being

older than 65 years. The majority of patients was male (61%), Caucasian (99%), and had stage M1c disease (61%). Forty-nine percent of patients failed ≥ 2 prior therapies.

With a median follow-up of 12.9 months (range, 0.6 to 20.1), the primary endpoint of confirmed best overall response rate (CR + PR) as assessed by an independent review committee (IRC) was 53% (95% CI: 44%, 62%). Median overall survival was 15.9 months (95% CI: 11.6, 18.3). The overall survival rate at 6 months was 77% (95% CI: 70%, 85%) and at 12 months was 58% (95% CI: 49%, 67%).

Nine of the 132 patients enrolled into NP22657 had V600K mutation positive tumours according to retrospective Sanger sequencing. Amongst these patients, 3 had a PR, 3 had SD, 2 had PD and one was not evaluable.

The European Medicines Agency has waived the obligation to submit the results of studies with vemurafenib in all subsets of the paediatric population in melanoma (see section 4.2 of the SmPC for information on paediatric use).

The results of the pivotal phase III study NO25026, and the supportive phase II study NP22657, were considered consistent and the CHMP considered that superiority of vemurafenib over dacarbazine had been demonstrated in the proposed indication: "Vemurafenib is indicated in monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma (see section 5.1)."

It is of note, however, that the median survival benefit in the confirmatory study is small (3.6 months at the latest data cut-off 03/10/11), possibly due to the cross over of patients at the time of the interim analysis, with a median OS of 9.9 month versus 13.2 months for dacarbazine and vemurafenib (HR 0.67; 95%CI 0.49 – 0.77; p=0.003), respectively.

The cobas 4800 BRAF V600 Mutation Test used in the pivotal trial is a real-time PCR assay that was designed to detect specifically the BRAFV600E mutation but will also detect other mutations such as V600K or V600D. The data on mutation analysis and OS are suggestive of a treatment benefit of vemurafenib on OS (HR 0.27; 95% CI: 0.05 – 1.51) and PFS (HR 0.09, 95% CI, 0.02, 0.45) in patients with the V600K mutation by Sanger sequencing.

Non-clinical data appear to support the limited clinical data on V600 mutations other than V600E. The clinical data indicated that vemurafenib inhibited BRAF with mutation V600E but results from the pivotal study showed that it may have also inhibited with V600K mutations. Hence, the CHMP evaluated the data and 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. The CHMP requested the applicant to perform further analyses on V600K mutation melanoma patients and other BRAF mutations not detected by the COBAS assay to better characterise the mechanism of action. This post authorisation measure is covered in the RMP.

It is important to note that there appears to be no benefit in patients which are BRAF WT. This is stated in the SmPC in section 4.2 where "Treatment with vemurafenib should be initiated and supervised by a qualified physician experienced in the use of anticancer medicinal products. Before taking vemurafenib, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test (see sections 4.4 and 5.1). " and in section 5.1 of the SmPC where it is stated that "Before taking vemurafenib, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test. In the phase II and phase III clinical trials, eligible patients were identified using a real-time polymerase chain reaction assay (the cobas 4800 BRAF V600 Mutation Test). This test has CE marking and is used to assess the BRAF mutation status of DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumour tissue. It was designed to detect the predominant BRAF V600E

mutation with high sensitivity (down to 5% V600E sequence in a background of wild-type sequence from FFPE-derived DNA). Non-clinical and clinical studies with retrospective sequencing analyses have shown that the test also detects the less common BRAF V600D mutations and V600K mutations with lower sensitivity. Of the specimens available from the non-clinical and clinical studies (n=467) that were mutation-positive by the cobas test and additionally analyzed by sequencing, no specimen was identified as being wild type by both Sanger and 454 sequencing."

There were too few non-caucasians to assess treatment benefit. A warning was introduced in the SmpC in section 4.2 of the SmPC.

Other guidance on vemurafenib treatment determined by the CHMP include:

Duration of treatment

Treatment with vemurafenib should continue until disease progression or the development of unacceptable toxicity (see table 1 below).

Missed doses

If a dose is missed, it can be taken up to 4 hours prior to the next dose to maintain the twice daily regimen. Both doses should not be taken at the same time.

Vomiting

In case of vomiting after vemurafenib administration the patient should not take an additional dose of the medicinal product but the treatment should be continued as usual.

2.5.4. Conclusions on the clinical efficacy

The pivotal trial NO25026 provided satisfactory evidence that vemurafenib prolonged OS and PFS in melanoma patients which were tested as BRAF V600 mutation positive in comparison with standard treatment dacarbazine. Efficacy has been demonstrated. The CHMP highlighted the fact that it is important that patients must be diagnosed a priori with BRAF V600 mutation-positive tumour status before taking vemurafenib. Based on the last data cut-off of 03/10/11, the benefits on OS and PFS appear established enough to exclude the confounding effect of the early interim analysis. The CHMP considers that more mature data on survival are required to better determine the magnitude of the long-term effect of vemurafenib treatment.

The CHMP considers the following measures should be provided as a condition for the marketing authorisation:

- Updated survival analyses from the pivotal trial NO25026.

2.6. Clinical safety

The safety analyses are based on data collected in 866 patients who received at least one dose of study drug, vemurafenib (N=584) or dacarbazine (N=282). Safety analyses were performed for the following studies or populations:

• The randomized Phase III study (NO25026; N=336 for vemurafenib and N=282 for dacarbazine)

• The pooled safety population (Phase 1 PLX06-02 and Phase 2 NP22657 studies; N=164)

• The Phase 2 study (NP22657; N=132)

• The melanoma extension cohort of the Phase 1 study (PLX06-02; N=32)

• Additional safety information from the supporting clinical pharmacology (NP25158; N=7, NP22676; N=25 and NP25163; N=52)

The safety population was defined as all treated patients who had at least one on-study assessment.

Patient exposure

As of the clinical cut-off date 30/12/10, the median total cumulative dose was 159 grams for vemurafenib vs 2000 mg/m^2 for dacarbazine. The median duration of treatment was 3.1 months (94.4 days) in the vemurafenib group and 0.76 months (23.1 days) in the dacarbazine group (time from first to last of the infusions given once every 3 weeks).

The median total daily vemurafenib dose was1.87 g/day. The median dose intensities (defined as the total actual dose taken divided by the total planned dose between dates of first and last dose) were 97.6% in the vemurafenib group vs 95.8% in the dacarbazine group. A summary of patient exposure is shown in Table 30.

The median number of cycles of dacarbazine was 2 with a median of 1000 mg/m^2 dacarbazine received per cycle.

Table 30 Summary of Extent of Exposure to RO5185426, Phase III [NO25026] Study and pooled safety population from phase I-II – safety population

	RO5185426 (N=336)	Pooled (N=164)
Length of Time on Treatment (Months) (a)		
Mean	3.45	6.1
SD	2.04	3.0
Median	3.09	6.4
25% and 75%-ile	1.72-4.86	3.8-8.1
Min,Max	0.03-9.30	0.1.13.7
Total Cumulative Dose of RO5185426 (gram)		
Mean	172.655	318.56
SD	106.699	162.94
Median	159.360	304.08
25% and 75%-ile	83.040-243.840	198.96-426.72
Min,Max	1.920-528.000	7.68-792.96
Average Dosage of RO5185426 per Day over Treatment Period (gram) (b)		
Mean	1.669	1.63
SD	0.315	0.33
Median	1.874	1.77
25% and 75%-ile	1.440-1.920	1.42-1.91
Min,Max	0.689-1.920	0.63-1.92
Dose Intensity (%) (c)		
0 – 75	86 (25.6%)	43 (26.2%)
75 – 90	57 (17.0%)	31 (18.9%)
90 – 100	193 (57.4%)	90 (54.9%)
Dose Intensity (%) (c)		
Mean	86.9	85
SD	16.4	17.2
Median	97.6	92
25% and 75%-ile	75.0-100.0	74-100
Min,Max	35.9-100.0	33-100

a. Length of time on treatment is defined as (last dose date - first dose date + 1), converted into months.
b. Average dosage of RO5185426 per day over treatment period = (cumulative doses / length of time on treatment) in days.
c. Dose Intensity = (total actual dose taken / total planned dose over time period from first to last dose) * 100%.

Adverse events

The most commonly reported AEs in the vemurafenib group were in the body system of skin and subcutaneous tissue disorders, where 90% of patients had at least one AE versus 19% in the dacarbazine group. The most commonly occurring AEs in this body system were rash, alopecia, and photosensitivity reaction (≥ 30% each vs ≤ 4% in the dacarbazine group). Gastrointestinal disorders also occurred frequently and with an overall similar incidence in the two groups (63% vemurafenib, 65% dacarbazine). Table 31 shows a summary of ADRs that are >10% in the vemurafenib treatment arm.

Table 31 Summary of ADRs* Occurring in ≥ 10% in the Vemurafenib Treatment Arm – safety population

ADRs	Phase III Study: Treatment Naive Patients						Phase II Study: Patients who Failed at least One Prior Systemic Therapy		
	Vemurafenib n= 336			Dacarbazine n= 282			Vemurafenib n= 132		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Skin and subcutaneous tissue disorders									
Rash	36	8	-	1	-	-	52	7	-
Photosensitivity reaction	30	3	-	4	-	-	49	3	-
Alopecia	35	<1	-	2	-	-	36	-	-
Pruritis	22	1	-	1	-	-	30	2	-
Hyperkeratosis	20	1	-	-	-	-	28	-	-
Rash maculo-papular	9	2	-	<1	-	-	21	6	-
Actinic keratosis	6	-	-	3	-	-	17	-	-
Dry skin	16	-	-	1	-	-	16	-	-
Rash popular	4	<1	-	-	-	-	13	-	-
Erythema	11	-	-	1	-	-	8	-	-
Musculoskeletal and connective tissue disorders									
Arthralgia	49	3	-	3	<1	-	67	8	-
Myalgia	12	-	-	1	-	-	24	<1	-
Pain in extremity	13	<1	-	6	2	-	9	-	-
Musculoskeletal pain	6	<1	-	3	-	-	11	-	-
Back pain	6	-	-	5	-	-	11	<1	-
General disorders and administration site conditions									
Fatigue	33	2	-	31	2	-	54	4	-
Oedema peripheral	15	<1	-	5	-	-	23	-	-
Pyrexia	18	<1	-	9	<1	-	17	2	-
Gastrointestinal disorders									
Nausea	30	1	-	41	2	-	37	2	-
Diarrhoea	25	<1	-	12	<1	-	29	<1	-
Vomiting	15	1	-	24	1	-	26	2	-
Constipation	10	-	-	23	-	-	16	-	-
Nervous system disorders									
Headache	21	<1	-	9	-	-	27	-	-
Dysgeusia	13	-	-	3	-	-	11	-	-
Neoplasms benign, malignant and unspecified (incl cysts									

ADRs	Phase III Study: Treatment Naive Patients						Phase II Study: Patients who Failed at least One Prior Systemic Therapy		
	Vemurafenib n= 336			Dacarbazine n= 282			Vemurafenib n= 132		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
and polyps)									
Skin papilloma	18	<1	-	-	-	-	30	-	-
SCC of skin[#]	12	11	-	<1	<1	-	21	21	-
Seborrhoeic keratosis	7	<1	-	1	-	-	14	-	-
Investigations									
Gamma-glutamyltransferase increased	4	2	<1	1	-	-	15	6	4
Metabolism and nutrition disorders									
Decreased appetite	16	-	-	7	-	-	21	-	-
Respiratory, thoracic and mediastinal disorders									
Cough	7	-	-	6	-	-	12	-	-
Injury, poisoning and procedural complications									
Sunburn	9	-	-	-	-	-	14	-	-

***** adverse drug reactions, reported using MedDRA and graded using NCI-CTCAE v 4.0 (NCI common toxicity criteria) for assessment of toxicity.

[#] all cases of cutaneous squamous cell carcinoma were to be reported as Grade 3 per instructions to study investigators and no dose modification or interruption was required.

Summary of the safety profile

The most common adverse drug reactions (ADR) (> 30%) reported with vemurafenib include arthralgia, fatigue, rash, photosensitivity reaction, nausea, alopecia and pruritus. CuSCC was very commonly reported and was most commonly treated by local excision.

Tabulated summary of adverse reactions

ADRs which were reported in melanoma patients are listed below by MedDRA body system organ class, frequency and grade of severity. The following convention has been used for the classification of frequency:

Very common ≥ 1/10

Common ≥ 1/100 to < 1/10

Uncommon ≥ 1/1,000 to < 1/100

Rare ≥ 1/10,000 to < 1/1000

Very rare < 1/10,000

In this section, ADRs are based on results in 500 patients from a phase III randomized open label study in adult patients with BRAF V600 mutation-positive unresectable or stage IV melanoma, as well as a phase II single-arm study in patients with BRAF V600 mutation-positive stage IV melanoma who had previously failed at least one prior systemic therapy (see section 5.1). All terms included are based on the highest percentage observed among phase II and phase III clinical trials. Within each frequency grouping, ADRs are presented in order of decreasing severity and were reported using NCI-CTCAE v 4.0 (common toxicity criteria) for assessment of toxicity.

Table 32: Clinically relevant ADRs occurring in patients treated with vemurafenib in the phase II or phase III study

System organ class	***Very Common***	***Common***	***Uncommon***
Infections and infestations		Folliculitis	
Neoplasms benign, malignant and unspecified (including cysts and polyps)	SCC of the skin [(c)], seborrheic keratosis, skin papilloma	Basal cell carcinoma	
Metabolism and nutrition disorders	Decreased appetite		
Nervous system disorders	Headache, dysgeusia	7th nerve paralysis	Neuropathy peripheral
Eye disorders		Uveitis	Retinal vein occlusion
Vascular disorders			Vasculitis
Respiratory, thoracic and mediastinal disorders	Cough		
Gastrointestinal disorders	Diarrhoea, vomiting, nausea, constipation		
Skin and subcutaneous tissue disorders	Photosensitivity reaction, actinic keratosis, rash, rash maculo-papular, rash papular, pruritus, hyperkeratosis, erythema, alopecia, dry skin, sunburn	Palmar-plantar erythrodysaesthesia syndrome,erythema nodosum, keratosis pilaris	Toxic epidermal necrolysis [(d)], Stevens-Johnson syndrome [(e)]
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia, pain in extremity, musculoskeletal pain, back pain	Arthritis	
General disorders and administration site conditions	Fatigue, pyrexia, oedema peripheral, asthenia		
Investigations	GGT increase [(b)]	ALT increase [(b)], alkaline phosphatase increase [(b)], bilirubin increase [(b)], weight decreased	AST increase [(b)]

The majority of patients in both treatment groups had AEs that were Grade 1/mild in intensity (94% vemurafenib, 78% dacarbazine) or Grade 2/moderate in intensity (78% vemurafenib, 51% dacarbazine).

A greater percentage of patients had AEs of Grade 3 or above in the vemurafenib group (50%) than the dacarbazine group (30%). The most common AEs ≥ Grade 3 in the vemurafenib group were (preferred terms): SCC of skin (11%) and rash (8%); the most common in the dacarbazine group were neutropenia (9%) and decreased neutrophil count (4%). Fewer Grade 4 events were reported in the vemurafenib group (4%) compared to the dacarbazine group (8%). The incidence of Grade 5 events was similar (2%) in both treatment groups. Grade 4 AEs in the vemurafenib group included:

pulmonary embolism (3 patients), increased GGT (2 patients), increased blood creatine phosphokinase (CPK), increased blood bilirubin, increased lipase, ageusia, intraventricular haemorrhage, pneumonia, pneumothorax, respiratory distress, neutropenia (all 1 patient each). As of the clinical cut-off, five vemurafenib patients had a total of six Grade 4 AEs that were considered by the investigator to be related to treatment (blood bilirubin increase, gamma glutamyltransferase increase, ageusia, blood creatine phosphokinase increase, neutropenia).

A summary of AEs of grade 3, 4, and 5 is shown in Table 33.

Table 33 Adverse Events of Grade 3, 4, 5 Occurring in ≥ 2% of Patients in Either Treatment Group - Safety Population

Body System/ Adverse Event	Dacarbazine N = 282 No. (%)	Vemurafenib N = 336 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	86 (30)	168 (50)
Total Number of AEs	144	308
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
SQUAMOUS CELL CARCINOMA OF SKIN	1 (<1)	38 (11)
KERATOACANTHOMA	-	20 (6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
RASH	-	28 (8)
PHOTOSENSITIVITY REACTION	-	9 (3)
RASH MACULO-PAPULAR	-	8 (2)
INVESTIGATIONS		
NEUTROPHIL COUNT DECREASED	10 (4)	-
GAMMA-GLUTAMYLTRANSFERASE INCREASED	-	9 (3)
BLOOD ALKALINE PHOSPHATASE INCREASED	-	7 (2)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
NEUTROPENIA	24 (9)	1 (<1)
THROMBOCYTOPENIA	6 (2)	2 (<1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
FATIGUE	5 (2)	6 (2)
GASTROINTESTINAL DISORDERS		
NAUSEA	5 (2)	4 (1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
ARTHRALGIA	2 (<1)	11 (3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
DYSPNOEA	8 (3)	2 (<1)

Serious adverse event/deaths/other significant events

As of the cut-off date 30/12/10, SAEs were reported by 33% of vemurafenib patients and 16% of dacarbazine patients. There were 110 vemurafenib patients that reported a total of 157 SAEs. Of these 157 SAEs, the majority (116/157 [74%]) were considered related to study drug by the investigator. The most common SAEs in the vemurafenib group were (preferred terms): SCC of the skin (11%) and keratoacanthoma (7%); all cases of these SAEs were considered drug related by the investigator.

A summary of AE and grade of AE is shown in Table 34 and 35.

Table 34: Overview of Adverse Events - Phase III [NO25026] Study and pooled Safety Population

Adverse Events	Dacarbazine (N = 282)		RO5185426 (N = 336)		Pooled Safety Population (N=164)	
	Number (%) of Patients					
Any Aes	253	(90)	326	(97)	164	(100)
Treatment-related Aes	194	(69)	316	(94)	162	(99)
AEs of Grade ≥ 3	86	(30)	168	(50)	123	(75)
Treatment-related AEs of Grade ≥ 3	53	(19)	143	(43)	102	(62)
Deaths†	66*	(23)	42*	(13)	41	(25)
Deaths within 28 days of last dose of study drug†	16	(5.5)	22	(6.5)	16	(10)
SAEs	45	(16)	110	(33)	85	(52)
Treatment-related SAEs	15	(5)	88	(26)	64	(39)
AEs that led to withdrawal from treatment	12	(4)	19	(6)	4	(2)
AEs that led to dose modification/interruption	44	(16)	129	(38)	94	(57)

* In the dacarbazine arm, 63 of the 66 deaths were due to disease progression; in the RO5185426 group, 35 of the 42 deaths were due to disease progression.
† Deaths were based on the all-treated population, where the N= 289 for dacarbazine and N = 336 for RO5185426.
Sources: ,

Table 35: Summary of Treatment-related AEs of Grade ≥ 3 with an Incidence ≥ 2% in any Group Phase III – [NO25026] and pooled Safety Population

Adverse Event	DTIC N = 282 No.(%)	RO5185426 N = 336 No.(%)	Pooled N=164 No.(%)
SQUAMOUS CELL CARCINOMA OF SKIN	1 (0.4)	38 (11.3)	38 (23.2)
BASAL CELL CARCINOMA			9 (5.5)
RASH		28 (8.3)	10 (6.1)
NEUTROPENIA	24 (8.5)	1 (0.3)	
KERATOACANTHOMA	-	20 (6.0)	7 (4.3)
ARTHRALGIA	2 (0.7)	11 (3.3)	9 (5.5)
DYSPNOEA	8 (2.8)	2 (0.6)	
NEUTROPHIL COUNT DECREASED	10 (3.5)	-	
GAMMA-GLUTAMYLTRANSFERA SE INCREASED	-	9 (2.7)	14 (8.5)
FATIGUE			4 (2.4)
PHOTOSENSITIVITY REACTION	-	9 (2.7)	6 (3.7)
RASH MACULO-PAPULAR	-	8 (2.4)	9 (5.5)
THROMBOCYTOPENIA	6 (2.1)	2 (0.6)	
BLOOD ALKALINE PHOSPHATASE INCREASED	-	7 (2.1)	4 (2.4)
ALANIN AMINOTRANSFERASE INCREASED			7 (4.3)

A summary of deaths for both treatment arms is presented in Table 36.

Table 36 Summary of Deaths by Primary Cause - Phase III [NO25026] Study and pooled safety population

Primary Cause of Death	DTIC N = 289 No.(%)	RO5185426 N = 336 No.(%)	Pooled N=164 No.(%)
Total No. of Deaths	66 (23)	42 (13)	53 (32)
Deceased within 28 days	16 (5.5)	22 (6.5)	20 (12)
DISEASEPROGRESSION	63 (22)	35 (10)	50 (30)
OTHER	2 (<1)	3 (<1)	2 (1)
ADVERSE EVENTS	1 (<1)	2 (<1)	
UNKNOWN	-	2 (<1)	

Significant adverse events

Stevens-Johnson Syndrome

There was one patient in the vemurafenib treated group who had Stevens-Johnson Syndrome. The event was considered related to vemurafenib by the investigator and resolved when vemurafenib was discontinued.

Cutaneous small cell carcinoma

Cases of cuSCC have been reported in patients treated with vemurafenib. The incidence of cuSCC in vemurafenib-treated patients across studies was approximately 20%. The phase III study, out of the 62 patients analysed the mean and median time to first occurrence of cuSCC was 8.3 weeks and 7.1 weeks, respectively; (range: 2.7 to 24.9 weeks). CuSCC usually occurred early in the course of treatment with a median time to the first appearance of 7 to 8 weeks. Of the patients who experienced cuSCC, approximately 33% experienced > 1 occurrence with median time between occurrences of 6 weeks.

The majority of the excised lesions reviewed by an independent central dermatopathology laboratory were classified as SCC-keratoacanthoma subtype or with mixed-keratoacanthoma features (52%). Most lesions classified as "other" (43%) were benign skin lesions (e.g. verruca vulgaris, actinic keratosis, benign keratosis, cyst/benign cyst).

There were 34 patients (55%) that received the prescribed daily dose (960 mg bid), 25 (40%) were receiving less than the prescribed dose, and three patients (5%) were receiving slightly more than the prescribed daily dose, when they experienced their first occurrence of cuSCC. All but 1 case of cuSCC adverse events in the vemurafenib group were considered related to treatment by the investigator. Cases of cuSCC were typically managed with simple excision, and patients generally continued on treatment without dose modification (see SmPC sections 4.2 and 4.4 of the SmPC). Summary of data are shown in Table 37.

Patients aged ≥ 65 years had approximately 2.5- to 5-times greater chance of developing cuSCC compared to those <65 years of age.

Table 37 Summary of Extent of Exposure to RO5185426 by Patients with or without cuSCC - Phase III (NO25026) study and Pooled Safety Population

	Phase III (NO25026) study		Pooled study	
	with cuSCC (N=62)	without cuSCC (N=274)	with cuSCC (N=42)	without cuSCC (N=122)
Length of Time on Treatment (Months) (a)				
Mean	4.46	3.22	7.1	5.8
SD	1.96	1.99	2.8	3.0
Median	4.22	2.79	7.0	5.7
25% and 75%-ile	3.32-5.59	1.45-4.60	5.0-9.7	3.5-7.8
Min,Max	0.76-9.00	0.03-9.30	1.7-13.0	0.1-13.7
Total Cumulative Dose of RO5185426 (gram)				
Mean	226.428	160.487	373.74	299.56
SD	104.848	103.483	157.88	160.93
Median	228.720	139.200	375.00	280.56
25% and 75%-ile	155.520-309.360	82.560-228.480	283.20-494.40	179.76-401.28
Min,Max	25.920-443.520	1.920-528.000	69.12-758.40	7.68-792.96
Average Dosage of RO5185426 per Day over Treatment Period (gram) (b)				
Mean	1.659	1.671	1.64	1.63
SD	0.284	0.322	0.34	0.33
Median	1.729	1.885	1.80	1.77
25% and 75%-ile	1.432-1.920	1.440-1.920	1.49-1.91	1.40-1.91
Min,Max	0.927-1.920	0.689-1.920	0.63-1.92	0.73-1.92

a. Length of time on treatment is defined as (last dose date - first dose date + 1), converted into months.
b. Average dosage of RO5185426 per day over treatment period = (cumulative doses / length of time on treatment) in days.
c. Dose Intensity = (total actual dose taken / total planned dose over time period from first to last dose) * 100%.

New primary melanoma

New primary melanomas have been reported in clinical trials. These cases were managed with excision, and patients continued treatment without dose adjustment. Monitoring for skin lesions should occur as outlined in section 4.4 of the SmPC.

Rash

Rash AEs were reported in 202 patients (60%) in the vemurafenib group and 10 patients (4%) in the dacarbazine group. Most rash AEs were Grade 1 or and were considered treatment related by the investigator. None resulted in discontinuation from treatment but about 54 of 250 events (22%; in the vemurafenib group) led to dose modification or interruption.

Photosensitivity

Photosensitivity AEs were reported in 124 patients (37%) in the vemurafenib group and 10 patients (4%) in the dacarbazine group in the pivotal trial. Almost all of the events were considered drug related by the investigator. None resulted in discontinuation from treatment. A summary of the photosensitivity AEs is presented in Table 38.

Table 38 Summary of "Photosensitivity" Adverse Events - (Phase III [NO25026] Study and Pooled Safety Population)

PHOTOSENSITIVITY	Phase III NO25026 study (N=336) Number (%)	Pooled safety population (N=164) Number (%)
Total Pts With at Least one AE	124 (37)	100 (61)
Total Number of AEs	132	108
PHOTOSENSITIVITY REACTION	101 (30)	81 (49)
SUNBURN	31 (8.9)	27 (16.5)
CTC grading		
Grade 1	82 (62)	72 (67)
Grade 2	40 (30)	30 (28)
Grade ≥ 3	9 (7)	6 (4)
Time to first onset (weeks)		
Median	1.7	3.5
Min-Max	0.1-20.1	0.3-36.7
Number of events resulting in a dose modification or interruption	3 (2)	5 (5)

Qt prolongation

Adverse events potentially associated with prolongation of cardiac repolarisation or arrhythmia occurred in 28 patients (8%) in the vemurafenib group and 16 patients (6%) in the dacarbazine group in the phase III study.

A summary of QT prolongation-related AE is shown in Table 39.

Table 39 Summary of Adverse events which could be potentially related to a QT Prolongation Safety Population

Body System/ Adverse Event	**CTC Grading**					
	Total No(%)	1 No(%)	2 No(%)	3 No(%)	4 No(%)	5 No(%)
Treatment: DTIC; N = 282						
QT PROLONGATION-RELATED AE						
Total Pts With at Least one AE	16 (6)	13 (5)	2 (<1)	1(<1)	-	-
DIZZINESS	10 (4)	10 (4)	-	-	-	-
SYNCOPE	3(1)	1 (<1)	1 (<1)	1 (<1)	-	-
LOSS OF CONSCIOUSNESS	2 (<1)	1 (<1)	1 (<1)	-	-	-
VENTRICULAR TACHYCARDIA	1 (<1)	1 (<1)	-	-	-	-
Total Number of AEs	16	13	2	1	-	-
Treatment: vemurafenib; N = 336						
QT PROLONGATION-RELATED AE						
Total Pts With at Least one AE	28 (8)	21 (6)	6 (2)	3(<1)	-	-

DIZZINESS	20 (6)	17 (5)	3 (<1)	-	-	-
ELECTROCARDIOGRAM QT PROLONGED	6 (2)	4 (1)	2(<1)	-	-	-
SYNCOPE	3 (<1)	-	1(<1)	2(<1)	-	-
LOSS OF CONSCIOUSNESS	1 (<1)	-	-	1(<1)	-	-
Total Number of AEs	30	21	6	3	-	-

Analysis of centralized ECG data from an open-label uncontrolled phase II QT sub-study in 132 patients dosed with vemurafenib 960 mg twice daily (NP22657) showed an exposure-dependent QTc prolongation. The mean QTc effect remained stable between 12-15 ms beyond the first month of treatment, with the largest mean QTc prolongation (15.1 ms; upper 95% CI: 17.7 ms) observed within the first 6 months (n=90 patients). Two patients (1.5%) developed treatment-emergent absolute QTc values >500 ms (CTC Grade 3), and only one patient (0.8%) exhibited a QTc change from baseline of >60 ms (see section 4.4 of the SmPC).

Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylaxis have been reported in association with vemurafenib. Severe hypersensitivity reactions may include Stevens-Johnson syndrome, generalized rash, erythema or hypotension. In patients who experience severe hypersensitivity reactions, vemurafenib treatment should be permanently discontinued (see section 4.4).

Other clinically meaningful AEs

The following events were considered as clinically meaningful events (ADRs) in the Phase 1 PLX06-02, Phase 2 NP22657, and Phase III NO25026 studies:

- Skin and Subcutaneous Tissue Disorders: keratosis pilaris, erythema nodosum, Stevens-Johnson syndrome
- Musculoskeletal and connective tissue disorders: arthritis
- Nervous system disorders: dizziness, neuropathy peripheral, facial (VIIth) nerve paralysis
- Neoplasms benign, malignant and unspecified: basal cell carcinoma
- Infections and infestations: folliculitis
- Investigations: weight decreased
- Eye disorders: retinal vein occlusion (RVO), uveitis
- Vascular disorders: vasculitis

The following rare but clinically meaningful AEs (ADRs) were also reported: facial (VIIth) nerve paralysis (four events total: one in Phase III study NO25026 and three in Phase 2 study NP22657), uveitis (11 events total; four in Phase III study NO25026, five in Phase 2 study NP22657, and two in Phase 1 study PLX06-02), and RVO (one event in Phase 2 study NP22657).

Laboratory findings

Liver function abnormality AEs were reported in 18% of vemurafenib patients in the Phase III NO25026 study, 34% of patients in the pooled safety population, and 24% of patients across the three clinical pharmacology studies. Among those patients who developed liver function abnormality AEs, the mean time to first onset was 6 to 7 weeks and the median 3 to 6 weeks. A summary liver abnormalities is shown in Table 40.

Table 40 Summary of Adverse Events of Liver Function Abnormalities - Safety Population

Body System / Adverse Event	**CTC Grading**					
Treatment: DTIC; N = 282	**Total No. (%)**	**1**	**2**	**3**	**4**	**5**
LIVER FUNCTION ABNORMALITIES						
Total Pts With at Least one AE	13 (5)	5 (2)	6 (2)	4 (1)	-	-
ALANINE AMINOTRANSFERASE INCREASED	3 (1)	1 (<1)	1 (<1)	1 (<1)	-	-
GAMMA-GLUTAMYLTRANSFERASE INCREASED	3 (1) -	2 (<1)	1 (<1)	-	-	-
ASCITES	2 (<1)	-	2 (<1)	-	-	-
ASPARTATE AMINOTRANSFERASE INCREASED	2 (<1)	2 (<1)	-	-	-	-
HYPOALBUMINAEMIA	2 (<1)	-	1 (<1)	1 (<1)	-	-
BLOOD BILIRUBIN INCREASED	1 (<1)	-	-	1 (<1)	-	-
HEPATIC ENZYME INCREASED	1 (<1)	-	-	1 (<1)	-	-
HEPATIC PAIN	1 (<1)	-	1 (<1)	-	-	-
LIVER PALPABLE SUBCOSTAL	1 (<1)	1 (<1)	-	-	-	-
TRANSAMINASES INCREASED	1 (<1)	-	1 (<1)	-	-	-
Total Number of AEs	17	6	7	4	-	-
Treatment: vemurafenib; N = 336						
LIVER FUNCTION ABNORMALITIES						
Total Pts With at Least one AE	59 (18)	28 (8)	20 (6)	25 (7)	3 (<1)	-
BLOOD ALKALINE PHOSPHATASE INCREASED	25 (7)	12 (4)	5 (1)	7 (2)	-	-
ALANINE AMINOTRANSFERASE INCREASED	18 (5)	12 (4)	3 (<1)	3 (<1)	-	-
ASPARTATE AMINOTRANSFERASE INCREASED	15 (4)	6 (2)	7 (2)	2 (<1)	-	-
BLOOD BILIRUBIN INCREASED	15 (4)	7 (2)	5 (1)	2 (<1)	1 (<1)	-
GAMMA-GLUTAMYLTRANSFERASE INCREASED	12 (4)	-	3 (<1)	7 (2)	2 (<1)	-

HYPERBILIRUBINAEMIA	6 (2)	3 (<1)	1 (<1)	2 (<1)	-	-
TRANSAMINASES INCREASED	4 (1)	2 (<1)	1 (<1)	1 (<1)	-	-
ASCITES	2 (<1)	1 (<1)	-	1 (<1)	-	-
BILIRUBIN CONJUGATED INCREASED	2 (<1)	-	1 (<1)	1 (<1)	-	-
HEPATIC ENZYME INCREASED	2 (<1)	1 (<1)	1 (<1)	-	-	-
LIVER FUNCTION TEST ABNORMAL	2 (<1)	-	-	2 (<1)	-	-
CHOLESTASIS	1 (<1)	-	-	1 (<1)	-	-
HEPATIC PAIN	1 (<1)	-	1 (<1)	-	-	-
HYPOALBUMINAEMIA	1 (<1)	-	-	1 (<1)	-	-
Total Number of AEs	106	44	28	30	3	-

Post-baseline increases in laboratory parameters to Grade 3 or 4 were uncommon; most occurred in <5% of patients. Laboratory parameters where post-baseline increases to Grade 3 or 4 occurred in ≥ 5% of patients included:

- decreased neutrophils: <1% vemurafenib group, 13% dacarbazine
- increased GGT: 11% vemurafenib, 9% dacarbazine
- decreased WBC: <1% vemurafenib, 6% dacarbazine
- decreased lymphocytes: 8% vemurafenib, 7% dacarbazine

Hepatic enzyme increase
Liver enzyme abnormalities reported in the phase III clinical study are expressed below as the proportion of patients who experienced a shift from baseline to a grade 3 or 4 liver enzyme abnormalities:

- Very common: GGT
- Common: ALT, alkaline phosphatase, bilirubin
- Uncommon: AST

There were no increases to Grade 4 ALT, alkaline phosphatase or bilirubin.

Safety in special populations

There was no evidence that any increases in AEs on vemurafenib compared to dacarbazine were greater in one gender subgroup than the other. Within the vemurafenib treatment group, the incidences of Grade ≥ 3 AEs of rash and other skin and subcutaneous tissue disorders, photosensitivity, and arthralgia were higher in female patients than male patients.

A summary of the AEs by age group is shown in Table 41.

Table 41 Adverse Events Occurring in ≥ 10% of Patients in any Subgroup by Age - Phase III [NO25026] Study and Pooled Safety Population

Body System SOC	Total Pts with at Least one AE			
	Phase 3 [NO25026] Study		Pooled Safety Study	
	<65 years N = 242 No. (%)	>=65 years N = 94 No. (%)	<65 years N = 135 No. (%)	>=65 years N = 29 No. (%)
Gastrointestinal Disorders	156 (64)	57 (61)	100 (74)	19 (66)
Skin And Subcutaneous Tissue Disorders	223 (92)	79 (84)	130 (96)	27 (93)
General Disorders And Administration Site Conditions	152 (63)	61 (65)	100 (74)	24 (83)
Musculoskeletal And Connective Tissue Disorders	172 (71)	53 (56)	118 (87)	24 (83)
Nervous System Disorders	110 (45)	42 (45)	76 (56)	22 (76)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	96 (40)	48 (51)	72 (53)	21 (72)
Infections And Infestations	83 (34	18 (19)	71 (53)	16 (55)
Metabolism And Nutrition Disorders	44 (18)	30 (32)	61 (45)	19 (66)
Blood And Lymphatic System Disorder	26 (11)	6 (6)	28 (21)	5 (17)
Psychiatric Disorders	33 (14)	18 (19)	29 (21)	9 (31)
Vascular Disorders	31 (13)	12 (13)	23 (17)	7 (24)
Injury, Poisoning And Procedural Complications	38 (16)	14 (15)	33 (24)	12 (41)
Eye Disorders	42 (17)	11 (12)	39 (29)	7 (24)
Investigations	69 (29)	24 (26)	66 (49)	14 (48)
Respiratory, Thoracic And Mediastinal Disorders	54 (22)	20 (21)	52 (39)	10 (34)
Renal And Urinary Disorders	13 (5)	5 (5)	22 (16)	8 (28)
Reproductive System And Breast Disorders	21 (9)	3 (3)	18 (13)	2 (7)
Cardiac Disorders	12 (5)	15 (16)	10 (7)	1 (3)
Total	**235 (97)**	**91 (97)**	**135 (100)**	**29 (100)**

Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Source ae11_agetrt_scs, ae11_agegrp

For AEs of Grade ≥ 3 intensity (NO25026), patients ≥ 65 years old, compared to patients <65 years old, experienced a higher incidence of preferred terms: SCC of the skin (19% vs. 8%, respectively, rash (13% vs. 7%, respectively), and GGT increased (4% vs 2%, respectively). For AEs of Grade ≥ 3 intensity, patients < 65 years old, compared to patients ≥ 65 years old, experienced a higher incidence of photosensitivity (4% vs 0%, respectively) and maculopapular rash (3% vs 1%, respectively). Each of these events occurred in a higher percentage of patients in the vemurafenib group than in the dacarbazine group.

Patients < 65 years reported a higher rate of Grade ≥ 3 (NO25026):

- decreased haemoglobin (5.6% vs 3%)
- increased alkaline phosphatase (4% vs 2%)
- increased ALT (4% vs 0%)

For AEs of Grade ≥ 3 intensity (pooled safety population), the incidence of neoplasms (benign, malignant, and unspecified; (59% vs 21%), metabolism and nutrition disorders (21% vs 9%), and renal and urinary disorders (10% vs 2%) was greater in older patients than younger patients, respectively.

Patients < 65 years of age reported a higher rate of Grade ≥ 3 (pooled safety analysis):

- decreases in GGT (24% vs 15%)
- increases in ALP (6% vs none reported)

Patients ≥ 65 years of age reported a higher rate of Grade ≥ 3:

- decreases in lymphocytes (28% vs 16%)
- decreases in potassium (14% vs 3%)
- decreases in phosphate (7% vs 2%)
- decreases in glucose (7% vs 2%)

Safety related to drug-drug interactions and other interactions

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

Discontinuation due to adverse events

As of the cut-off date 30/12/10, AEs that led to withdrawal of treatment occurred in 19 patients (6%) in the vemurafenib group and 12 patients (4%) in the dacarbazine group.

Shock

One patient (1402) discontinued vemurafenib treatment for safety reasons in the supporting clinical pharmacology study. The patient developed shock on treatment day 8. Upon re-challenge with a single dose of 240 mg vemurafenib, the patient became hypotensive, but responded to resuscitation and was discharged from the hospital; study treatment was permanently discontinued.

Post marketing experience

The applicant did not submit reports on post-marketing experience with vemurafenib.

2.6.1. Discussion on clinical safety

The safety database comprises of 584 patients which have been treated with at least one dose of vemurafenib. Most patients on vemurafenib experienced at least one AE (97%) during treatment but the majority was mild and manageable. The most common AEs reported in vemurafenib treated patients were rash, photosensitivity reaction, alopecia, arthralgia and fatigue. The most common adverse events of grade 3 and 4 were rash and sensitivity and arthralgia.

Almost half of the patients (44.6%) experienced a dose reduction or treatment interruption as a consequence of an AE. The most common cause for discontinuation of vemurafenib was disease progression. It should be noted that the AEs appear to occur early with a median of 7 weeks. Because of the short duration of treatment (median 4 months) there is lack of safety data for long-term exposure to vemurafenib. This is acceptable as there will be further updates on safety.

There is a risk that other malignancies have not been detected because of the short exposure. There is a lack of safety data regarding the non-caucasian population. This has been noted in section 4.2 of the SmPC.

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

It is contraindicated to take vemurafenib in patients with hypersensitivity to the active substance or to any of the excipients.

Before taking vemurafenib, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test. The efficacy and safety of vemurafenib in patients with tumours expressing BRAF V600 non-E mutations have not been convincingly established (see section 5.1 of the SmPC). Vemurafenib should not be used in patients with wild type BRAF malignant melanoma.

Hypersensitivity reaction

Serious hypersensitivity reactions, including anaphylaxis have been reported in association with vemurafenib (see sections 4.3 and 4.8 of the SmPC). Severe hypersensitivity reactions may include Stevens-Johnson syndrome, generalized rash, erythema or hypotension. In patients who experience severe hypersensitivity reactions, vemurafenib treatment should be permanently discontinued.

Dermatologic Reactions

Severe dermatologic reactions have been reported in patients receiving vemurafenib, including rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis in the pivotal clinical trial. In patients who experience a severe dermatologic reaction, vemurafenib treatment should be permanently discontinued.

QT prolongation

Exposure-dependent QT prolongation was observed in an uncontrolled, open-label phase II study in previously treated patients with metastatic melanoma (see section 4.8 of the SmPC). QT prolongation may lead to an increased risk of ventricular arrhythmias including Torsade de Pointes. Treatment with vemurafenib is not recommended in patients with uncorrectable electrolyte abnormalities (including magnesium), long QT syndrome or who are taking medicinal products known to prolong the QT interval.

Electrocardiogram (ECG) and electrolytes (including magnesium) must be monitored in all patients before treatment with vemurafenib, after one month of treatment and after dose modification.

Further monitoring is recommended in particular in patients with moderate to severe hepatic impairment monthly during the first 3 months of treatment followed by every 3 months thereafter or more often as clinically indicated. Initiation of treatment with vemurafenib is not recommended in patients with QTc>500 milliseconds (ms). If during treatment the QTc exceeds 500 ms, vemurafenib treatment should be temporarily interrupted, electrolyte abnormalities (including magnesium) should be corrected, and cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias) should be controlled. Re-initiation of treatment should occur once the QTc decreases below 500 ms and at a lower dose as described in Table 1. Permanent discontinuation of vemurafenib treatment is recommended if the QTc increase meets values of both > 500 ms and >60 ms change from pre-treatment values.

Ophthalmologic reactions

Serious ophthalmologic reactions, including uveitis, iritis and retinal vein occlusion, have been reported. Monitor patients routinely for ophthalmologic reactions.

Cutaneous Squamous Cell Carcinoma (cuSCC)

Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been reported in patients treated with vemurafenib (see section 4.8). It is recommended that all patients receive a dermatologic evaluation prior to initiation of therapy and be monitored routinely while on therapy. Any suspicious skin lesions should be excised, sent for dermatopathologic evaluation and treated as per local standard of care. The prescriber should examine the patient monthly during

and up to six months after treatment for cuSCC. In patients who develop cuSCC, it is recommended to continue the treatment without dose adjustment. Monitoring should continue for 6 months following discontinuation of vemurafenib or until initiation of another anti-neoplastic therapy. Patients should be instructed to inform their physicians upon the occurrence of any skin changes.

Non-Cutaneous Squamous Cell Carcinoma (non-cuSCC)

No cases of non-cuSCC have been reported in clinical trials with vemurafenib in melanoma. Patients should undergo a head and neck examination, consisting of at least a visual inspection of oral mucosa and lymph node palpation prior to initiation of treatment and every 3 months during treatment.

In addition, patients should undergo a chest Computerised Tomography (CT) scan, prior to treatment and every 6 months during treatment.

Anal examinations and pelvic examinations (for women) are recommended before and at the end of treatment or when considered clinically indicated.

Following discontinuation of vemurafenib, monitoring for non-cuSCC should continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to clinical practices.

New primary melanoma

New primary melanomas have been reported in clinical trials. Cases were managed with excision and patients continued treatment without dose adjustment. Monitoring for skin lesions should occur as outlined above for cutaneous squamous cell carcinoma.

Liver injury

Liver laboratory abnormalities may occur with vemurafenib (see section 4.8). Liver enzymes (transaminases and alkaline phosphatase) and bilirubin should be monitored before initiation of treatment and monthly during treatment, or as clinically indicated. Laboratory abnormalities should be managed with dose reduction, treatment interruption or with treatment discontinuation (see sections 4.2 and 4.4).

Hepatic impairment

No adjustment to the starting dose is needed for patients with hepatic impairment. Patients with mild hepatic impairment due to liver metastases without hyperbilirubinaemia may be monitored according to the general recommendations. There are only very limited data available in patients with moderate to severe hepatic impairment. Patients with moderate to severe hepatic impairment may have increased exposure (see section 5.2). Thus close monitoring is warranted especially after the first few weeks of treatment as accumulation may occur over an extended period of time (several weeks). In addition ECG monitoring every month during the first three months is recommended.

Renal impairment

No adjustment to the starting dose is needed for patients with mild or moderate renal impairment. There are only limited data available in patients with severe renal impairment (see section 5.2 of the SmPC). Vemurafenib should be used with caution in patients with severe renal impairment and patients should be closely monitored.

Photosensitivity

Mild to severe photosensitivity was reported in patients who received vemurafenib in clinical studies (see section 4.8). All patients should be advised to avoid sun exposure while taking vemurafenib. While taking the medicinal product, patients should be advised to wear protective clothing and use a broad

spectrum Ultraviolet A (UVA)/Ultraviolet B (UVB) sunscreen and lip balm (Sun Protection Factor ≥ 30) when outdoors to help protect against sunburn.

For photosensitivity grade 2 (intolerable) or greater, dose modifications are recommended (see section 4.2).

Effects of vemurafenib on other medicinal products

Vemurafenib may increase the plasma exposure of medicinal products predominantly metabolized by CYP1A2 and decrease the plasma exposure of medicines predominantly metabolized by CYP3A4, including oral contraceptives. Dose adjustments for medicinal products medications predominantly metabolized via CYP1A2 or CYP3A4 should be considered based on their therapeutic windows before concomitantly treating with vemurafenib (see sections 4.5 and 4.6).

Exercise caution and consider additional INR (International Normalized Ratio) monitoring when vemurafenib is used concomitantly with warfarin.

Effect of other medicinal products on vemurafenib

Vemurafenib pharmacokinetics could be affected by medicines that inhibit or influence P-gp (e.g. verapamil, clarithromycin, cyclosporine, ritonavir, quinidine, dronedarone, amiodarone, itraconazole, ranolazine) (see section 4.5).

Concomitant administration of potent inducers of P-gp, glucuronidation, CYP3A4 (e.g. rifampicin, rifabutin, carbamazepine, phenytoin or St John's Wort [hypericin]) should be avoided when possible (see section 4.5). Alternative treatment with less inducing potential should be considered to maintain the efficacy of vemurafenib.

Women of chidbearing potential / Contraception in females

Women of childbearing potential have to use effective contraception during treatment and for at least 6 months after treatment.

Vemurafenib might decrease the efficacy of hormonal contraceptives (see section 4.5 of the SmPC).

Pregnancy

There are no data regarding the use of vemurafenib in pregnant women.

Vemurafenib revealed no evidence of teratogenicity in rat or rabbit embryo/foetuses (see section 5.3). In animal studies, vemurafenib was found to cross the placenta. Vemurafenib should not be administered to pregnant women unless the possible benefit to the mother outweighs the possible risk to the foetus.

Breastfeeding

It is not known whether vemurafenib is excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue vemurafenib therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

No specific studies with vemurafenib have been conducted in animals to evaluate the effect on fertility. However, in repeat-dose toxicity studies in rats and dogs, no histopathological findings were noted on reproductive organs (see section 5.3 of the SmPC).

The effects of vemurafenib on the ability to drive and use machines have not been studied. Patients should be made aware of the potential fatigue or eye problems that could be a reason for not driving.

Dermatologic Reactions

Severe dermatologic reactions have been reported in patients receiving vemurafenib, including rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis in the pivotal clinical trial. In patients who experience a severe dermatologic reaction, vemurafenib treatment should be permanently discontinued.

Special populations

Elderly

In the phase III study, ninety-four (28%) of 336 patients with unresectable or metastatic melanoma treated with vemurafenib were ≥ 65 years. Elderly patients (≥ 65 years) may be more likely to experience adverse reactions, including cuSCC, decreased appetite, and cardiac disorders.

Gender

During clinical trials with vemurafenib, grade 3 adverse reactions reported more frequently in females than males were rash, arthralgia and photosensitivity.

There is no specific antidote for overdose of vemurafenib. Patients who develop adverse reactions should receive appropriate symptomatic treatment. No cases of overdose have been observed with vemurafenib in clinical trials. In case of suspected overdose, vemurafenib should be withheld and supportive care initiated.

2.6.2. Conclusions on the clinical safety

The AES reported for patients being treated with vemurafenib appear to be mostly of low grade and manageable. It was noted that cuSCC was predominantly found in vemurafenib treated patients after a short exposure to the drug. The CHMP considered that with an early detection program and intervention, the safety issue of cuSCC was adequately managed.

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.

Risk Management Plan

The applicant submitted a risk management plan.

Table 41 Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Important Identified Risks		
Cutaneous SCC	Routine Pharmacovigilance Cumulative review in each scheduled PSUR. Additional Pharmacovigilance SCC Semi-Annual Report: Monitor the number of patients who discontinue treatment due to SCC to evaluate whether excisions are diligently performed. Monitor the number of SCC adverse events to evaluate whether frequency reported is consistent with frequency in clinical trials and current proposed risk management is appropriate. Epidemiology Study: The primary objective of this study is to examine the incidence of cutaneous SCC among a cohort of Kaiser Permanente of Northern California (KPNC) members diagnosed with melanoma from January 1, 2000 – December 31, 2005. A secondary aim is to examine how relevant co-variates including patient characteristics such as age, gender, and race/ethnicity; melanoma tumour characteristics such clinical subtype, invasiveness, stage and location, and care of tumour such as surgery, chemotherapy and radiation impact outcome (SCC). A third aim is to assess the interaction between variables known to affect melanoma risk and variables pertinent to SCC outcome including size, location, degree of	Routine: Patient Education in the PIL Prescriber Education in the SmPC: Section 4.4 of the SmPC: *Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been reported in patients treated with vemurafenib.* *It is recommended that all patients receive a dermatologic evaluation prior to initiation of therapy and be monitored routinely while on therapy. Any suspicious skin lesions should be excised, sent for dermatopathologic evaluation and treated as per local standard of care. In patients who develop cuSCC, it is recommended to continue the treatment without dose adjustment. Monitoring should continue for 6 months following discontinuation of vemurafenib or until initiation of another anti-neoplastic therapy. Patients should be instructed to inform their physicians upon the occurrence of any skin changes.* Section 4.8 of the SmPC: *Cases of cuSCC have been reported in patients treated with vemurafenib. The incidence of cuSCC in vemurafenib-treated patients across studies was approximately 20%. The majority of the excised lesions reviewed by an independent central dermatopathology laboratory were classified as SCC-keratoacanthoma subtype or with mixed-keratoacanthoma features (52%). Most lesions classified as "other" (43%) were benign skin lesions (e.g. verruca vulgaris, actinic keratosis, benign keratosis, cyst/benign cyst). CuSCC usually occurred early in the course of treatment with a median time to the first appearance of 7 to 8 weeks. Of the patients who experienced cuSCC, approximately 33% experienced > 1 occurrence with median time between occurrences of 6 weeks. Cases of cuSCC were typically managed with simple excision, and patients generally continued on treatment without dose modification*

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
	differentiation, KA-type and invasiveness. <u>Pre-clinical Exploratory Research to further characterise cu SCC:</u> To address further the mechanism of action underlying the development of cuSCC related to vemurafenib treatment from a non-clinical perspective. Prospective, observational safety study of patients with BRAF v600 mutation-positive unresectable or metastatic melanoma treated with vemurafenib. MO25515 An open-label, multicenter study to assess the safety of RO5185426 in patients with metastatic melanoma	
Liver Injury	<u>Routine Pharmacovigilance</u> Cumulative review in each scheduled PSUR. Prospective, observational safety study of patients with BRAF v600 mutation-positive unresectable or metastatic melanoma treated with vemurafenib.	<u>Routine</u>: Patient Education in the PIL Prescriber Education in the SmPC <u>Section 4.2 of the SmPC:</u> *Dose modification schedule:* *Grade 1 and tolerable Grade 2AE:* *Maintain 960 mg twice daily dose.* *Grade 2 (intolerable) or Grade3* *First occurrence of any grade 2 or 3 AE:* *Interrupt treatment until Grade 0-1, then resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).* *Second occurrence of any grade 2 or grade 3 AE or persistence after treatment interruption:* *Interruption until Grade 0-1, then resume dosing at 480 mg twice daily (or discontinure permanently if the dose has already been lowered to 480 mg twice daily).* *Third occurrence of any grade 2 or 3 AE or persistence after 2nd dose reduction:* *Discontinue permanently.* *Grade 4*

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
		First occurrence of any grade 4 AE: *Discontinue permanently or interrupt until Grade 0-1. Resume dosing at 480 mg twice daily dose (or discontinue permanently if the dose has already been lowered to 480 mg twice daily)* *Second occurrence of any grade 4 AE or persistence of any grade 4 AE after first dose reduction:* *Discontinue permanently .* <u>Section 4.4 of the SmPC:</u> *Liver laboratory abnormalities may occur with vemurafenib. Liver enzymes (transaminases and alkaline phosphatase) and bilirubin should be monitored before initiation of treatment and monthly during treatment, or as clinically indicated. Laboratory abnormalities should be managed with dose reduction, treatment interruption or with treatment discontinuation.* <u>Section 4.8 of the SmPC:</u> *Liver enzyme abnormalities reported in the Phase III clinical study are expressed below as the proportion of patients who experienced a shift from baseline to a grade 3 or 4 liver enzyme abnormalities.* • *Very common: GGT* • *Common: ALT, alkaline phosphatase, bilirubin* • *Uncommon: AST* *There were no increases to Grade 4 ALT, alkaline phosphatase or bilirubin.*
Photosensitivity / Sunburn	<u>Routine Pharmacovigilance</u> Cumulative review in each scheduled PSUR.	<u>Routine:</u> Patient Education in the PIL Prescriber Education in the SmPC <u>Section 4.2 of the SmPC:</u> *Dose modification schedule* *Grade 1 and tolerable Grade 2:Maintain 960 mg twice daily dose* *Grade 2 (intolerable) or Grade 3* *First occurrence of any grade 2 or 3 AE:* *Interruption until Grade 0-1,resume dosing at 720 mg twice daily,(or 480 mg twice daily if the dose has already been lowered).* *Second occurrence of any grade 2 or 3 AE or persistence after treatment interruption:* *Interrupt treatment until Grade 0-1, then resume at 480mg* *Third occurrence of any grade 2 or 3 AE or persistence after 2nd dose reduction:* *Discontinue permanently.* *Grade 4* *First occurrence of any grade 4 AE:*

Safety Concern	**Proposed Pharmacovigilance Activities (Routine and Additional)**	**Proposed Risk Minimisation Activities (Routine and Additional)**
		Discontinue permanently or interrupt until Grade 0-1. Resume dosing at 480 mg twice daily dose (or discontinue permanently if the dose has already been lowered to 480 mg twice daily) *Second occurrence of any grade 4 AE or persistence of any grade 4 AE after first dose reduction:* *Discontinue permanently .*
Arthralgia	<u>Routine Pharmacovigilance</u> Cumulative review in each scheduled PSUR.	<u>Routine</u>: Patient Education in the PIL Prescriber Education in the SmPC <u>Section 4.2 of the SmPC:</u> *Dose modification schedule:* *Grade 1 and tolerable Grade 2:* *Maintain 960 mg twice daily dose* *Grade 2 (intolerable) or Grade 3* *First occurrence of any grade 2 or 3 AE:* *Interruption until Grade 0-1, then resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered)* *Second occurrence of any grade 2 or 3 AE or persistence after treatment interruption* *Interrupt treatment until grade 0 – 1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily)* *Third occurrence of any grade 2 or 3 AE or persistence after 2nd dose reduction* *Discontinue permanently* *Grade 4* *First occurrence of any grade 4 AE* *Discontinue permanently or interrupt until Grade 0-1. Then resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480mg twice daily.* *Second occurrence of any grade 4 AE or persistence of any grade 4 AE after first dose reduction:* *Discontinue permanently .* <u>Section 4.8 of the SmPC:</u> Listed as an adverse drug reaction.
Rash	<u>Routine Pharmacovigilance</u> Cumulative review in each scheduled PSUR.	<u>Routine</u>: Patient Education in the PIL Prescriber Education <u>Section 4.2 of the SmPC:</u> *Dose modification schedule:* *Grade 1 and tolerable Grade 2* *Maintain 960 mg twice daily dose:* *Grade 2 (intolerable) or Grade 3* *First occurrence of any grade 2 or 3 AE:*

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
		Interruption until Grade 0-1, then resume at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered) *Second occurrence of any grade 2 or 3 AE or persistence after treatment interruption:* *Interruption until Grade 0-1, then resume at 480 mg twice daily(or discontinue permanently if the dose has already been lowered to 480 mg twice daily).* *Third occurrence of any grade 2 or 3 AE or persistence after second dose reduction* *Discontinue permanently* *Grade 4* *First occurrence of any grade 4 AE* *Discontinue permanently of- interrupt until Grade 0-1 then resume at 480 mg twice daily(or discontinue permanently if the dose has already been lowered to 480 mg twice daily).* *Second occurrence of any grade 4 AE or persistence of any grade 4 AE or persistence of any grade 4 AE after first dose reduction* *Discontinue permanently* <u>Section 4.8 of the SmPC:</u> Listed as an adverse drug reaction.
Fatigue	<u>Routine Pharmacovigilance</u> Cumulative review in each scheduled PSUR.	<u>Routine</u>: Patient Education in the PIL Prescriber Education in the SmPC <u>Section 4.2 of the SmPC:</u> *Dose modification schedule:* *Grade 1 and tolerable Grade 2* *Maintain 960 mg twice daily dose* *Grade 2 (intolerable) or Grade 3* *First occurrence of any grade 2 or 3 AE:* *Interruption until Grade 0-1, then resume at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).* *Second occurrence of any grade 2 or 3 AE or persistence after treatment interruption* *Interruption until Grade 0-1, then resume at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).* *Third occurrence of any grade 2 or 3 AE or persistence after 2nd dose reduction* *Discontinue permanently* *Grade 4* *First occurrence of any grade 4 AE* *Discontinue permanently or interrupt until Grade 0-1 then resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily.* *Second occurrence of any grade 4 AE or persistence of any grade 4 AE after first dose*

Safety Concern	**Proposed Pharmacovigilance Activities (Routine and Additional)**	**Proposed Risk Minimisation Activities (Routine and Additional)**
		reduction *Discontinue permanently* <u>Section 4.8 of the SmPC:</u> Listed as an adverse drug reaction.
QTc prolongation	<u>Routine Pharmacovigilance</u> Cumulative review in each scheduled PSUR. Prospective, observational safety study of patients with BRAF v600 mutation-positive unresectable or metastatic melanoma treated with vemurafenib. MO25515 An open-label, multicenter study to assess the safety of RO5185426 in patients with metastatic melanoma	<u>Routine</u>: Patient Education in the PIL Prescriber Education in the SmPC <u>Section 4.2 of the SmPC:</u> *Dose modification schedule:* QTc>500 ms at baseline: Treatment is not recommended. QTc increase meets values of both > 500 ms and >60 ms change from pre-treatment values: Discontinue permanently. 1st occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60 ms: Temporarily interrupt treatment until QTc decreases below 500 ms. See monitoring measures in section 4.4. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered). 2nd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60ms: Temporarily interrupt treatment until QTc decreases below 500 ms. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily) 3rd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60ms: Discontinue permanently *Exposure-dependent QT prolongation was observed in an uncontrolled, open-label phase II study in previously treated patients with metastatic melanoma. Management of QTc prolongation may require dose reduction, temporary interruption and/or treatment discontinuation* .<u>Section 4.4 of the SmPC:</u> *Exposure-dependent QT prolongation was observed in an uncontrolled, open-label phase II study in previously treated patients with metastatic melanoma (see section 4.8). QT prolongation may lead to an increased risk of ventricular arrhythmias including Torsade de Pointes. Treatment with vemurafenib is not recommended in patients with uncorrectable electrolyte abnormalities (including magnesium), long QT syndrome or who are taking medicinal products known to prolong the QT interval. Electrocardiogram (ECG) and electrolytes*

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
		(including magnesium) must be monitored in all patients before treatment with vemurafenib, after one month of treatment and after dose modification. Further monitoring is recommended in particular in patients with moderate to severe hepatic impairment monthly during the first 3 months of treatment followed by every 3 months thereafter or more often as clinically indicated. Initiation of treatment with vemurafenib is not recommended in patients with QTc>500 ms. If during treatment the QTc exceeds 500 milliseconds (ms), vemurafenib treatment should be temporarily interrupted, electrolyte abnormalities (including magnesium) should be corrected, and cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias) should be controlled. Re-initiation of treatment should occur once the QTc decreases below 500 ms and at a lower dose as described in Table 1. Permanent discontinuation of vemurafenib treatment is recommended if the QTc increase meets values of both > 500 ms and >60 ms change from pre-treatment values. <u>Section 4.8 of the SmPC:</u> *Analysis of centralized ECG data from an open-label uncontrolled Phase II QT sub-study in 132 patients dosed with vemurafenib 960 mg twice daily (NP22657) showed an exposure-dependent QTc prolongation. The mean QTc effect remained stable between 12-15 ms beyond the first month of treatment, with the largest mean QTc prolongation (15.1 ms; upper 95% CI: 17.7 ms) observed within the first 6 months (n=90 patients). Two patients (1.5%) developed treatment-emergent absolute QTc values >500 ms (CTC Grade 3), and only one patient (0.8%) exhibited a QTc change from baseline of >60 ms.*
Hypersensitivity and Severe Cutaneous Reactions	<u>Routine Pharmacovigilance</u> Cumulative review in each scheduled PSUR.	<u>Routine</u>: Patient Education in the PIL Prescriber Education in the SmPC <u>Section 4.2 of the SmPC:</u> *Dose modification schedule:* *Grade 1 and tolerable Grade 2* *Maintain 960 mg twice daily dose* *Grade 2 (intolerable) or Grade 3* *First occurrence of any grade 2 or 3 AE:* *Interruption until Grade 0-1, then resume at 720 mg twice daily dose (or 480 mg twice daily if the dose has already been lowered)* *Second occurrence of any grade 2 or 3 AE or persistence after treatment interruption* *Interruption until Grade 0-1, then resume at 480 mg twice daily dose (or discontinue permanently if the dose has already been lowered to 480 mg twice daily)*

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
		Third occurrence of any grade 2 or 3 AE or persistence after 2nd dose reduction *Discontinue permanently* *Grade 4* *First occurrence of any grade 4 AE* *Discontinue permanently or interrupt until Grade 0-1. Then resume at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily)* *Second occurrence of any grade 4 AE or persistence of any grade 4 AE after first dose reduction* *Discontinue permanently .* Section 4.4 of the SmPC: *Serious hypersensitivity reactions, including anaphylaxis have been reported in association with vemurafenib. Severe hypersensitivity reactions may include Stevens-Johnson syndrome, generalized rash, erythema or hypotension. In patients who experience severe hypersensitivity reactions, vemurafenib treatment should be permanently discontinued.* Section 4.4 of the SmPC: *Severe dermatologic reactions have been reported in patients receiving vemurafenib, including rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis in the pivotal clinical trial. In patients who experience a severe dermatologic reaction, vemurafenib treatment should be permanently discontinued.* Section 4.3 of the SmPC *Hypersensitivity to the active substance or to any of the excipients.* Section 4.8 of the SmPC: *Serious hypersensitivity reactions, including anaphylaxis have been reported in association with vemurafenib. Severe hypersensitivity reactions may include Stevens-Johnson syndrome, generalized rash, erythema or hypotension. In patients who experience severe hypersensitivity reactions, vemurafenib treatment should be permanently discontinued (see section 4.4).* *Dermatologic Reactions*(e) *Severe dermatologic reactions have been reported in patients receiving vemurafenib, including rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis in the pivotal clinical trial. In patients who experience a severe dermatologic reaction, vemurafenib treatment should be permanently discontinued.*

Safety Concern	**Proposed Pharmacovigilance Activities (Routine and Additional)**	**Proposed Risk Minimisation Activities (Routine and Additional)**
Uveitis	Routine Pharmacovigilance Cumulative review in each scheduled PSUR.	Routine: Patient education in the PIL Prescriber Education in the SmPC Section 4.2 of the SmPC: *Dose modification schedule:* *Grade 1 and tolerable Grade 2* *Maintain 960 mg twice daily dose* *Grade 2 (intolerable) or Grade 3* *First occurrence of any grade 2 or 3 AE* *Interruption until Grade 0-1, then resume at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered)* *Second occurrence of any grade 2 or 3 AE or persistence after treatment interruption* *Interruption until Grade 0-1, then resume at 480 mg twice daily (or discontinue permanently if the dose has already bee lowered to 480 mg twice daily)* *Third occurrence of any grade 2 or 3 AE or persistence after second dose reduction* *Discontinue permanently* *Grade 4* *First Occurrence of any Grade 4 AE* *Discontinue permanently or interrupt until Grade 0-1 then resume dosing at 480 mg twice daily dose (or discontinue permanently if the dose has already been lowered to 480 mg twice daily)* *Second occurrence of any grade 4 AE or persistence of any grade 4 AE after first dose reduction* *Discontinue permanently .* Section 4.8 of the SmPC: Listed as a common adverse drug reaction in vemurafenib treated patients in the Phase 2 and Phase 3 studies.
Retinal Vein Occlusion	Routine Pharmacovigilance Cumulative review in each scheduled PSUR.	Routine: Patient Education in the PIL Prescriber Education in the SmPC Section 4.2 of the SmPC: *Dose modification schedule:* *Grade 1 and tolerable Grade 2* *Maintain 960 mg twice daily dose* *Grade 2 (intolerable) or Grade 3* *First occurrence of any grade 2 or 3 AE* *Interruption until Grade 0-1, then resume at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).* *Second occurrence of any grade 2 or 3 AE or*

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
		persistence after treatment interruption *Interruption until Grade 0-1, then resume at 480 mg twice daily dose (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).* *Third occurrence of any grade 4 AE* *Discontinue permanently* *Grade 4-* *First occurrence of any grade 4 AE* *Discontinue permanently or interrupt until Grade 0-1 then resume at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily)* *Second occurrence of any grade 4 AE or persistence of any grade 4 AE after first dose reduction* *Discontinue permanently* <u>Section 4.8 of the SmPC:</u> Listed as an uncommon adverse drug reaction in vemurafenib treated patients in the Phase 2 and Phase 3 studies.
Important Potential Risks		
Non-Cutaneous Squamous Cell Carcinoma	<u>Routine Pharmacovigilance</u> Cumulative review in each scheduled PSUR. <u>Additional Pharmacovigilance</u> <u>SCC Semi-Annual Report:</u> Monitor the number of patients who discontinue treatment due to SCC to evaluate whether excisions are done diligently. Monitor the number of SCC adverse events to evaluate whether frequency reported is consistent with frequency in clinical trials and current proposed risk management is appropriate. Prospective, observational safety study of patients with BRAF v600 mutation-positive unresectable or metastatic melanoma treated with vemurafenib. MO25515 An open-label, multicenter study to assess the safety of RO5185426 in patients with	<u>Routine</u>: Patient Education in the PIL Prescriber Education in the SmPC <u>Section 4.2 of the SmPC:</u> *Dose modification schedule:* *Grade 1 and tolerable Grade 2* *maintain 960 mg twice daily dose* *Grade 2 (intolerable) or Grade 3* *First Occurrence of any grade 2 or 3 AE* *Interruption until Grade 0-1, then resume at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).* *Second occurrence of any grade 2 or 3 AE or persistence after treatment interruption* *Interruption until Grade 0-1, then resume at 480 mg twice daily (or 480 mg twice daily if the dose has already been lowered).* *Third occurrence of any grade 2 or 3 AE or persistence after second dose* *Discontinue permanently* *Grade 4* *First occurrence of any grade 4 AE* *Discontinue permanently or interrupt until Grade 0-1 then resume dosing at 480 mg twice daily dose (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).* *Second occurrence of any grade 4 AE or persistence of any grade 4 AE after first dose reduction* *Discontinue permanently*

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
	metastatic melanoma	Section 4.4 of the SmPC: *No cases of non-cuSCC have been reported in clinical trials with vemurafenib in melanoma. Patients should undergo a head and neck examination, consisting of at least a visual inspection of oral mucosa and lymph node palpation prior to initiation of treatment and every 3 months during treatment.* *In addition, patients should undergo a chest Computerised Tomography (CT) scan, prior to treatment and every 6 months during treatment. Anal examinations and pelvic examinations (for women) are recommended before and at the end of treatment or when considered clinically indicated.* *Following discontinuation of vemurafenib, monitoring for non-cuSCC should continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to clinical practices*
VIIth Nerve Paralysis	Routine Pharmacovigilance Cumulative review in each scheduled PSUR.	Routine: Patient Education in the PIL Prescriber Education in the SmPC Section 4.2 of the SmPC: *Dose modification schedule:* *Grade 1 and tolerable Grade 2* *Maintain 960 mg twice daily dose* *Grade 2 (intolerable) or Grade 3* *First Occurrence of any grade 2 or 3 AE* *Interruption until Grade 0-1, then resume at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).* *Second occurrence of any grade 2 or 3 AE or persistence after treatment interruption* *Interruption until Grade 0-1, then resume at 480 mg twice daily (or 480 mg twice daily if the dose has already been lowered).* *Third occurrence of any grade 2 or 3 AE of persistence after second dose* *Discontinue permanently* *Grade 4* *First occurrence of any grade 4 AE* *Discontinue permanently or interrupt until Grade 0-1 then resume dosing at 480 mg twice daily dose (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).* *Second occurrence of any grade 4 AE or persistence of any grade 4 AE after first dose reduction* *Discontinue permanently* Section 4.8 of the SmPC:

Safety Concern	**Proposed Pharmacovigilance Activities (Routine and Additional)**	**Proposed Risk Minimisation Activities (Routine and Additional)**
		Listed as a common adverse drug reaction in vemurafenib treated patients in the Phase 2 and Phase 3 studies.
Bone Marrow Toxicity	Routine Pharmacovigilance Cumulative review in each scheduled PSUR.	Routine: Prescriber Education in the SmPC Section 5.3of the SmPC: *In an in vitro bone marrow cytotoxicity study, slight cytotoxicity was observed in some lympho-haematopoietic cell populations of rat, dog and human at clinically relevant concentrations.*
New Primary Melanoma	Routine Pharmacovigilance Cumulative review in each scheduled PSUR MO25515 protocol has been amended to include patient follow up for two years after last dose of vemurafenib	Routine. Prescriber Education in the SmPC Section 4.4 of the SmPC: *New primary melanomas have been reported in clinical trials. Cases were managed with excision and patients continued treatment without dose adjustment. Monitoring for skin lesions should occur as outlined above for cutaneous squamous cell carcinoma.* Section 4.8 of the SmPC: *New primary melanomas have been reported in clinical trials. These cases were managed with excision, and patients continued treatment without dose adjustment. Monitoring for skin lesions should occur as outlined in section 4.4.*
Drug – Drug Interaction	Routine Pharmacovigilance Study NP25396 (PAM) Interaction study with ketoconazole (PAM) Interaction study with rifampicin (PAM) Interaction study with digoxin (PAM) In vitro study of potential effect of vemurafenib on CYP2A6, CYP2B6, CYP2C8 and CYP2E1 activity (PAM) In vitro study on the effect of transport proteins (PAM)	Section 4.4, Special Warnings and Precautions for Use in the EU SmPC states the following: Vemurafenib may increase the plasma exposure of medicinal products predominantly metabolized by CYP1A2 and decrease the plasma exposure of medicines predominantly metabolized by CYP3A4, including oral contraceptives. Dose adjustments for medicinal products predominantly metabolized via CYP1A2 or CYP3A4 should be considered based on their therapeutic windows before concomitantly treating with vemurafenib (see sections 4.5 and 4.6). Exercise caution and consider additional INR (International Normalized Ratio) monitoring when vemurafenib is used concomitantly with warfarin. Vemurafenib pharmacokinetics could be affected by medicines that inhibit or influence P-gp (e.g. verapamil, clarithromycin, cyclosporine, ritonavir, quinidine, dronedarone, amiodarone, itraconazole, ranolazine). Concomitant administration of potent inducers of P-gp, glucuronidation, CYP3A4 (e.g. rifampicin, rifabutin, carbamazepine, phenytoin or St John's Wort [hypericin]) should be avoided when possible. Alternative treatment with less inducing potential should be considered to maintain the

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
		efficacy of vemurafenib. Section 4.5 Interaction with other medicinal products and other forms of interaction in the EU SmPC states the following: Effects of vemurafenib on CYP substrates CYP1A2 inhibition was observed when a single dose of caffeine was co-administered after repeat dosing with vemurafenib for 15 days. This resulted in an average 2.5-fold increase (maximum up to 10-fold) in caffeine plasma exposure after vemurafenib treatment. Vemurafenib may increase the plasma exposure of substances predominantly metabolized by CYP1A2 and dose adjustments should be considered. CYP3A4 induction was observed when a single dose of midazolam was co-administered after repeat dosing with vemurafenib for 15 days. This resulted in an average 32% decrease (maximum up to 80%) in midazolam plasma exposure after vemurafenib treatment. Vemurafenib may decrease the plasma exposure of substances predominantly metabolized by CYP3A4. On this basis, the efficacy of contraceptive pills metabolized by CYP3A4 used concomitantly with vemurafenib might be decreased. Dose adjustments for CYP3A4 substrates with narrow therapeutic window should be considered. Mild induction of CYP2B6 by vemurafenib was noted *in vitro* at a vemurafenib concentration of 10 µM. It is currently unknown whether vemurafenib at a plasma level of 100 µM observed in patients at steady state (approximately 50 µg/ml) may decrease plasma concentrations of concomitantly administered CYP2B6 substrates, such as bupropion. When a single dose of warfarin was co-administered after repeat dosing with vemurafenib for 15 days, some patients exhibited increased warfarin exposure (mean 20%) (see section 4.4). Caution should be exercised when vemurafenib is co-administered with warfarin (CYP2C9) in patients with melanoma. Due to the long half-life of vemurafenib, the full inhibitory effect of vemurafenib on a concomitant medicinal product might not be observed before 8 days of vemurafenib treatment. After cessation of vemurafenib treatment, a washout of 8 days might be necessary to avoid an interaction with a subsequent treatment. Effects of vemurafenib on substance transport systems

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
		In vitro studies have demonstrated that vemurafenib is an inhibitor of the efflux transporter (P-gp). The clinical relevance of this finding is unknown. It cannot be excluded that vemurafenib may increase the exposure of other medicines transported by P-gp. The possible effect of vemurafenib on other transporters (e.g. BCRP) is currently unknown. Effects of concomitant medicines on vemurafenib *In vitro* studies suggest that CYP3A4 metabolism and glucuronidation are responsible for the metabolism of vemurafenib. Biliary excretion appears to be another important elimination pathway. There are no clinical data available showing the effect of strong inducers or inhibitors of CYP3A4 and/or transport protein activity on vemurafenib exposure. Vemurafenib should be used with caution in combination with potent inhibitors of CYP3A4, glucuronidation and/or transport proteins (e.g. ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, nefazodone, atazanavir). Concomitant administration of potent inducers of P-gp, glucuronidation, and/or CYP3A4 (e.g. rifampicin, rifabutin, carbamazepine, phenytoin or St John's Wort [hypericum perforatum]) may lead to supoptimal exposure to vemurafenib and should be avoided. *In vitro* studies have demonstrated that vemurafenib is a substrate of the efflux transporter, P-gp. The effects of P-gp inducers and inhibitors on vemurafenib exposure are unknown. It cannot be excluded that vemurafenib pharmacokinetics could be affected by medicines that inhibit or influence P-gp (e.g. verapamil, clarithromycin, cyclosporine, ritonavir, quinidine, dronedarone, amiodarone, itraconazole, ranolazine). It is currently unknown whether vemurafenib is a substrate also to other transport proteins.
Important Missing Information		
Treatment of patients with severe hepatic impairment	<u>Routine Pharmacovigilance</u> Cumulative review in each scheduled PSUR <u>Additional pharmacovigilance</u>	<u>Routine</u>: Patient Education in the PIL Prescriber Education in the SmPC <u>Section 4.4 of the SmPC:</u> *No adjustment to the starting dose is needed for patients with hepatic impairment.* *Patients with mild hepatic impairment due to liver metastases without hyperbilirubinaemia may be*

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
	activity New study involving patients with severe hepatic impairment.	*monitored according to the general recommendations. There is only very limited data available in patients with moderate to severe hepatic impairment,* *Patients with moderate to severe hepatic impairment may have increased exposure (see section 5.2). Thus close monitoring is warranted especially after the first few weeks of treatment as accumulation may occur over an extended period of time (several weeks). In addition ECG monitoring every month during the first three months is recommended.* Section 5.2 of the SmPC: *Based on preclinical data and the human mass balance study, major part of vemurafenib is eliminated via the liver. In the population pharmacokinetic analysis using data from clinical trials in patients with metastatic melanoma, increases in AST and ALT up to 3 times Upper Limit of Normal did not influence the apparent clearance of vemurafenib. Data are insufficient to determine the effect of metabolic or excretory hepatic impairment on vemurafenib pharmacokinetics (see sections 4.2 and 4.4).*
Long Term Safety	Routine Pharmacovigilance Cumulative review in each scheduled PSUR. Additional pharmacovigilance activity The safety study protocol (MO25515) has been amended to include patient follow up for two years after last dose of vemurafenib	None
Treatment in patients aged 12 to 18 years of age	Routine Pharmacovigilance Cumulative review in each scheduled PSUR. Study NO25390	None
Second primary malignancy	Routine Pharmacovigilance Cumulative review in each scheduled PSUR.	None

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
	Additional pharmacovigilance activity The safety study protocol (MO25515) has been amended to include patient follow up for two years after the last dose of vemurafenib.	
Patients with low exposure	Routine Pharmacovigilance Additional pharmacovigilance activity Analyses Plan to address PAM Food effect Study NP25396	None

No additional risk minimisation activities were required beyond those included in the product information.

In addition, the CHMP considered that the applicant should take the following minor points into consideration when an update of the Risk management Plan is submitted:

- to provide with the next RMP update missing protocols of studies in the PhV plan

2.8. 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

Vemurafenib, an inhibitor of oncogenic BRAF V600E mutation, has shown a superior efficacy compared to dacarbazine in the pivotal phase III study N025026 in patients that have melanoma tumours that harbour the BRAFV600 mutation. The trial also showed a statistical significant improvement in PFS of approximately 4 months with 5.32 months vs 1.61 months (HR 0.26; CI 0.20 – 0.30; p<0.0001) (data cut-off 30/12/10) and an increase in OS of 3.6 months with 9.9 vs 13.2 months (HR 0.67; CI 0.54 – 0.84; p=0.0003) (uncensored data, data cut-off 03/10/11) for vemurafenib and dacarbazine

respectively. Subgroup analysis supported the co-primary efficacy endpoints. The CHMP considered that the survival data were clinically relevant and that clinical benefit had been demonstrated.

Uncertainty in the knowledge about the beneficial effects.

There is uncertainty in the knowledge of the long term benefit of vemurafenib in melanoma patients that harbour the BRAFV600 mutation and the impact of prognostic factors. This, however, does not affect the observed clinical relevant benefit for patients in OS and the positive benefit risk of vemurafenib in the proposed indication. No adverse efficacy outcome in the long-term is expected.

There is also a limited uncertainty over the PK/PD interaction data and the food effect on the bioavailability of vemurafenib. The CHMP was of the opinion that further fine tuning of the food effect was necessary as it had not been fully investigated prior to the start of the phase III study. There are studies currently ongoing and data will be submitted as part of RMP measures. The uncertainties have been mitigated through appropriate warning and specific advice in the SmPC and were considered to have no impact on the positive benefit risk balance.

Risks

Unfavourable effects

In the pivotal phase III trial, the major target organs for toxicity were skin, gastrointestinal, musculoskeletal and connective tissues. There were about 50% of the patients that experienced grade 3 adverse events in the vemurafenib treatment. The adverse events required dose modifications in about 40% of the patients and about 8% of patients had to discontinue treatment. The CHMP considered that appropriate wording in the SmPC was sufficient to identify and minimise the safety risks. Approximately 20% of patients treated with vemurafenib developed squamous cell carcinoma of the skin (cuSCC). The applicant has put in place a risk minimisation strategy in the RMP to ensure that cuSCC is an identified risk which can be captured early and treated in patients that receive vemurafenib.

Uncertainty in the knowledge about the unfavourable effects

There is some uncertainty with regards to patients with hepatic impairment. Given that vemurafenib is metabolised by the liver, this is important missing information which is included as a warning in the SmPC in section 4.4 and in the RMP. There is a planned study to address this safety issue which deadline for submitting the clinical study report is on the 31/08/2017.

Benefit-risk balance

Importance of favourable and unfavourable effects

The pivotal study NO25026 has shown a clinically relevant effect of vemurafenib for overall survival and 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. The risk for secondary neoplasms, such as cuSCC, exists but the magnitude of the risk is considered low. In addition, cuSCC can be managed in clinical practice. Appropriate wording in the SmPC and adequate RMP measures have been implemented.

Benefit-risk balance

Based on the results of the pivotal trial NO25026 and the supportive data from trial PLX06-02 and NP22657, the benefits of vemurafenib treatment in melanoma patients harbouring tumours with V600 mutations outweighed the adverse events (rash, arthralgia, fatigue and cuSCC). Therefore, the CHMP considers that the benefit-risk balance for vemurafenib in melanoma patients that harbour BRAF V600 mutation is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Zelboraf in the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma 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.

Conditions and requirements of the Marketing Authorisation

Risk Management System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 5.0 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

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

Not applicable

Obligation to complete post-authorisation measures

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
Updated survival analyses from the pivotal trial NO25026	31st May 2012

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, non-clinical and clinical properties of the active substance, the CHMP considers that vemurafenib is to be qualified as a new active substance.