Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Vemurafenib

Proprietary Product Name: Zelboraf

Sponsor: Roche Products Pty Limited

December 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

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

Contents

I. Introduction to product submission

Submission details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	April 2012
Active ingredient(s):	Vemurafenib
Product Name(s):	Zelboraf
Sponsor's Name	Roche Products Pty Limited
Dose form(s):	Tablet
Strength(s):	240 mg
Container(s):	Aluminium (Al/Al) blister pack
Pack size(s):	56 tablets
Approved Therapeutic use:	Zelboraf is indicated for the treatment of unresectable Stage IIIC or Stage IV metastatic melanoma positive for a BRAF V600 mutation
Route(s) of administration:	Oral
Dosage:	960 mg twice daily
ARTG Number (s)	183674

Product background

Roche Products Pty Ltd has applied to register the new chemical entity, vemurafenib (Zelboraf), for the treatment of patients with unresectable Stage IIIC or Stage IV metastatic melanoma whose tumours are positive for a BRAF V600 mutation. The proposed regimen is 960 mg (four 240 mg tablets) twice daily (equivalent to a total daily dose of 1920 mg).

Vemurafenib is an inhibitor of some mutated forms of BRAF kinase, including V600E. It inhibits proliferation and survival of cells with BRAF kinase mutations by suppressing signals in the mitogen-activated protein kinase (MAPK) pathway. Mutations in BRAF kinase, mostly V600E, occur in about half of patients with metastatic melanoma.

The rationale for identifying a compound that targets activating mutations in the BRAF gene is based on the prevalence of mutations in a variety of cancers, the most common of which results in a valine to glutamic acid substitution and residue 600 ($BRAF^{V600E}$). Oncogenic mutations in BRAF kinase predominantly V600E have been observed in approximately 8% of all solid tumours including 50% of metastatic melanomas. Recent biological insights and characterisation of the role of oncogenic BRAF mutations highlights the central role of this kinase in signalling pathways that control cellular proliferation. Oncogenic mutations in BRAF result in constitutive activation of BRAF kinase, which causes disregulated downstream signalling via MEK and ERK leading to excessive self-proliferation and survival.

The therapeutic relevance of oncogenic BRAF is an important target in melanoma and supported by several lines of evidence. Depletion of mRNA for oncogenic BRAF with small interfering RNA (siRNA) inhibits the growth of melanoma cell lines *in vitro* and the growth of tumours in human melanoma xenograft models. For these reasons, vemurafenib (VEM) was developed as a first in class selective low molecular weight orally bioavailable inhibitor of oncogenic BRAF kinase for the treatment of patients with metastatic melanoma. Given the target of activity of VEM the clinical development program was designed to evaluate the activity of VEM in patients whose tumours tested positive for $BRAF^{V600}$ mutations by a companion diagnostic test.

The cobas 4800 BRAF V600 Mutation Test, which was developed as a companion diagnostic test for VEM, is a real-time polymerase chain reaction (PCR) test intended to be used to select melanoma patients whose tumours carry $BRAF^{V600}$ mutations for treatment with VEM. It was designed to detect the predominant V600E mutation with high sensitivity.

The drug was given orphan designation for the proposed indication in Australia on 14 April 2011.

The proposed indication is dependent on the availability of an appropriate test for the BRAF V600 mutation. The test in the pivotal trials was the cobas 4800 BRAF V600 Mutation Test (Roche Molecular Systems Inc). [1]

The multikinase inhibitor, sorafenib (Nexavar), is a related drug. It inhibits BRAF V600 kinase and other kinases. It is used in hepatocellular and renal cell carcinoma.

The TGA adopted European Medicines Agency (EMA) *Guideline on the Evaluation of Anticancer Medicinal Products in Man*[2] is relevant to this application.

Regulatory status

Zelboraf has been approved in the regions shown in Table 1 below.

[1] Sponsor comment:'This test was approved in Australia on 25 November 2011."

[2] CPMP/EWG/205/95.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/12/WC500017748.pdf

Table 1. International regulatory status

Region	Approval date	Indication in the country
United States	17 August 2011	Zelboraf® is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation as detected by an FDA-approved test. Limitation of Use: Zelboraf is not recommended for use in patients with wild-type BRAF melanoma.
Switzerland	18 October 2011	Treatment of unresectable or metastatic melanoma patients with a BRAF V600 mutation.
Brazil	26 December 2011	Zelboraf (vemurafenib) is indicated for the treatment of BRAF V600E mutation-positive unresectable or metastatic melanoma, when detected by an ANVISA-approved test.
Israel	16 January 2012	Zelboraf is indicated for the treatment of BRAFV600 mutation-positive unresectable or metastatic melanoma.
Canada	15 February 2012	Zelboraf™ (vemurafenib) is indicated as a monotherapy for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma. A validated test is required to identify BRAF V600 mutation status.
New Zealand	16 February 2012	Zelboraf is indicated for the treatment of unresectable stage IIIC or stage IV metastatic melanoma positive for the BRAF V600 mutation.
European Union	17 February 2012	Vemurafenib is indicated in monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.
Mexico	20 February 2012	Zelboraf is indicated for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma.

Product Information

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

List of abbreviations

The following is a list of abbreviations used in this AusPAR:

PCR	polymerase chain reaction
PFS	progression free survival
OS	overall survival
IRC	independent review committee

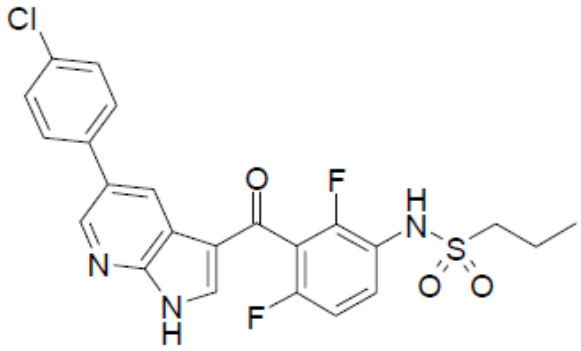
NCA	non compartmental analysis
PK	pharmacokinetics
CRC	colorectal cancer
DLT	dose limiting toxicity
CuSCC	cutaneous squamous cell carcinoma
MTD	maximum tolerated dose
AE	adverse event
BORR	best overall response rate
AESI	adverse events of special interest
KA	keratoacanthoma

II. Quality findings

Drug substance (active ingredient)

Vemurafenib is a substituted azaindole; it also contains a sulfonamide moiety but shows little structural relationship to 'sulfonamide' drugs (see Figure 1 below).

Figure 1. Chemical structure



vemurafenib

molecular formula: $C_{23}H_{18}ClF_2N_3O_3S$; molecular weight: 489.93

Vemurafenib is achiral and does not show stereoisomerism. Reported pKa values are 7.9 and 11.1 and the partition coefficient in water is 3.0. Aqueous solubility is very low and independent of pH.

There are multiple polymorphic forms; two forms were made and used in formulation development. Form I is crystalline but thermodynamically unstable, converting to Form II. Form II is more stable but less soluble, hence showing lower bioavailability. Vemurafenib polymorphism and particle size is not controlled as the drug is dissolved in tablet manufacture.

Related drugs

There are a number of tyrosine kinase inhibitors already registered in Australia: imatinib (Glivec); gefitinib (Iressa); erlotinib (Tarceva); sunitinib (Sutent); dasatinib (Sprycel), lapatinib (Tykerb); nilotinib (Tasigna); pazopanib (Votrient).
Vemurafenib is synthetic and observed impurity levels are low; the limit for each unspecified impurity should be tightened in keeping with guidelines[3], consistent with PSC advice. This could be made a condition of registration if necessary.

Because of the low solubility of the drug, it is stabilised in a non-crystalline form which shows significantly higher solubility, thereby enhancing *in vivo* absorption. Vemurafenib is processed with a polymer (hydroxypropyl methyl cellulose acetate succinate (HPMC-AS)) to form a micro precipitated bulk powder (MBP) (Vemurafenib/HPMC-AS).

Drug product

Zelboraf 240 mg tablets are oval, biconvex, pinkish-white to orange-white, film-coated tablets with VEM engraved on one side. The tablets are packed in aluminium blisters containing 56 tablets (one week's supply). Excipients are conventional. Tablets are made by granulation of the MBP using roller compaction. The proposed 240 mg tablet formulation was the same as that used in almost all clinical trials.

Tablet dissolution is controlled. There are limits for any crystalline drug in the tablets. No significant changes or trends were seen on tablet storage.

Biopharmaceutics

The Phase I dose ranging trial PLX06-02 used micronised, crystalline (Form I) vemurafenib filled into 100 and 300 mg capsules.
During product development two 40 mg capsule MBF formulations were developed. In a relative bioavailability study (PLX102-01), these 40 mg formulations showed similar bioavailability and increased in bioavailability compared to the Phase I (crystalline) capsules.
As the proposed tablet formulation was the same in almost all clinical trials (except for details of tablet engraving), bioequivalence with the capsules used in two Phase I studies (PLX06-02 and PLX102-01) was not considered an issue.
No absolute bioavailability information is available for humans. 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.
No study of the effect of food has been completed, a dedicated food effect study (NP25396) has been started, but the results have not been submitted. Fasting doses are recommended.

Advisory committee considerations

Pharmaceutical Subcommittee (PSC)

This application was considered at the 142nd meeting of the PSC of the Advisory Committee on Prescription Medicines (ACPM) (see Recommendation No. 2248). The PSC recommended tightening the limits for unspecified impurities in the drug substance.

The PSC considered that an absolute bioavailability study could have been undertaken using a micro-dose IV infusion.

[3] ICH Topic Q 3 A (R1) Impurities testing guideline. Impurities in new drug substances. CPMP/ICH/2737/99. http://www.tga.gov.au/pdf/euguide/ich273799en.pdf

The PSC was concerned about the lack of detailed TGA review of population pharmacokinetic studies in this and other applications. The Committee agreed that the attention of the Delegate and the ACPM should be drawn to the fact that the discussion on the effect of vemurafenib on QTc prolongation in the PI was not comprehensive as comments were made only on certain aspects of the population pharmacokinetic analysis provided in support of this submission.

Apart from some PI detail recommendations, the PSC considered that there should be no objection to registration on pharmaceutic and biopharmaceutic grounds.

Quality summary and conclusions

The attention of the ACPM was drawn to the incomplete information on absolute bioavailability study and on the effects of food. The limit on unspecified impurities in the drug substance could be tightened. Registration was otherwise recommended with respect to chemistry and biopharmaceutic aspects.

III. Nonclinical findings

Introduction

The submitted nonclinical data were in general accordance with the TGA adopted Eurpean Union (EU) guideline on the nonclinical evaluation of anticancer pharmaceuticals.[4] During the clinical development of vemurafenib, several formulations were examined in the nonclinical studies. The MBP formulation was eventually chosen as it gave greater and more predictable oral bioavailability. All pivotal pharmacology, repeat-dose toxicity and reproductive toxicity studies were conducted using the clinical MBP formulation. Unfortunately, the safety pharmacology studies were conducted with an earlier crystalline formulation in corn oil and there were no accompanying toxicokinetic data for relative exposure comparisons. In general, the exposures to vemurafenib were subclinical in the animal studies and, therefore, the full spectrum of safety issues has not been adequately addressed in the submitted data. This is considered a major limitation but for the most part was unavoidable as the maximum feasible dose was used in the majority of the pivotal toxicity studies.

Pharmacology

Primary pharmacodynamics

Rationale and mechanism of action

The MAPK (Mitogen-Activated Protein Kinase) pathway is a phosphorylation-driven signal transduction pathway that couples intracellular responses to the binding of growth factors to cell surface receptors. This pathway regulates several processes including cell proliferation and differentiation. The classical MAPK pathway consists of RAS, RAF, MEK and ERK where RAS triggers the formation of the RAF/MEK/ERK kinase complex. The MAPK pathway is frequently activated in human cancers. An activating mutation in the gene encoding the serine–threonine protein kinase BRAF occurs in 40 to 60% of melanomas and 7 to 8% of all cancers. Oncogenic mutations in the *BRAF* gene result in constitutive activation of BRAF kinase. Ninety percent of reported BRAF mutations result in a substitution of glutamic acid for valine at amino acid 600 (the V600E mutation). This BRAF mutation constitutively activates BRAF and downstream signal transduction in the MAP kinase pathway. Vemurafenib was designed as an inhibitor of BRAF V600 mutants.

[4]EMEA/CHMP/ICH/646107/2008 ICH Topic S9. Nonclinical Evaluation for Anticancer Pharmaceuticals http://www.tga.gov.au/pdf/euguide/swp64610708enfin.pdf

Inhibition of this mutated BRAF is intended to inhibit downstream signalling and reduce cell proliferation and inhibit tumour growth.

In vitro studies

In vitro pharmacology studies investigated kinase inhibition, inhibition of downstream signalling and inhibition of cell proliferation. Vemurafenib inhibited the kinase activity of wild-type BRAF kinase and the following mutants V600E, V600A, V600D, V600K, V600M, V600R, V600G, E586K, F595L, G464V, G469A, K601E and T599I with 50 % inhibitory concentration (IC_{50}) values ≤110 nM. This inhibitory potency is below the clinical plasma concentrations (167 nM, free fraction[5]).

BRAF V600E mutants constitutively activate the downstream ERK and MEK signalling pathways. Vemurafenib at concentrations at or below the clinical C_{max} inhibited ERK and/or MEK phosphorylation in melanoma and other tumour cell lines expressing BRAF V600E, V600D or V600R. No significant effect was seen on phosphorylation in cells expressing BRAF G469V at concentrations up to 30 μM (~180 times the clinical free plasma concentrations). In contrast, at 240 nM vemurafenib (~1.5 times the clinical free plasma concentration) both ERK and MEK phosphorylation were induced in cells expressing wild-type BRAF.

When tested with 17 human melanoma cell lines, vemurafenib inhibited the proliferation of all lines expressing BRAF V600 mutations (V600D, V600E, V600K and V600R). The IC_{50} values ranged from 15 to 1000 nM (0.1–6 times the free clinical plasma concentration). Similar inhibitory activity was seen in a breast cancer cell line expressing BRAF V600E. No significant effect was seen on the proliferation of other tumour cell types (lung, gastric, breast, pancreatic and skin) which contained wild-type BRAF, BRAF G469V, G466V or G464V (IC_{50} >10 μM; ~60 times the clinical plasma concentration).

In vivo

The efficacy of vemurafenib was assessed in mouse xenograft tumour models bearing human melanoma grafts. Three different tumour lines were examined. Greater than 100% tumour growth inhibition and complete regression was seen in all mice bearing melanoma tumours expressing BRAF V600E treated with 75–100 mg/kg orally (PO) twice a day (bd) for 11–21 days. Life span was increased 61–3500% in these animals. The area under the plasma concentration time curve from 2 to 24 h ($AUC_{2\text{-}24h}$) was ~0.5 times the clinical $AUC_{0\text{-}24h}$ at the maximum clinical dose, thus supporting the proposed indication. In one of these models, tumours recurred over time, suggesting that the tumour may have gained resistance to vemurafenib. Vemurafenib at doses up to 100 mg/kg PO bd also had some efficacy (based on tumour growth inhibition, partial and complete regression) in colorectal tumour xenografts that express BRAF V600E. As exposures in this study were not reported and significant differences in bioavailability were seen, depending on formulation, it is difficult to compare the levels of vemurafenib in this study with the proposed clinical dose. Vemurafenib had no effect on colorectal tumours expressing wild-type BRAF at concentrations up to 100 mg/kg PO bd. Efficacy against melanomas expressing wild-type BRAF was not examined.

Development of resistance

The development of resistance was assessed in human melanoma cell lines cultured for 3 months. The IC_{50} values increased from 71 nM to 8.5 μM (51 times the free clinical peak plasma concentration (C_{max})). Resistant cells retained the BRAF V600E mutation and investigations suggested multiple factors may be involved in resistance. In particular, a

[5] Based on clinical steady state plasma levels (C_{ss}) of 119 μM (58.5 μg/mL) and a plasma free fraction of 0.14%.

number of lines had acquired RAS mutations and RAS-GTP levels were elevated. Down-regulation of *KRAS* expression increased the sensitivity of resistant lines carrying a K117N mutation of KRAS (2 to 6 fold decrease in IC_{50} was seen). When this resistant line was implanted on nude mice, no inhibition of tumour growth was seen after vemurafenib treatment (25 mg/kg/day PO for 11 days). One hundred percent tumour growth inhibition was seen when the same experiment was conducted with the sensitive parental line. Tumour growth inhibition (TGI; 98%) and increased life span (ILS; 100%) was seen in mice bearing the resistant line when vemurafenib treatment was combined with treatment with a MEK inhibitor. The results were superior to those obtained with a MEK inhibitor alone (44% TGI, 33% ILS). Other reported mechanisms of resistance to vemurafenib treatment include induction or persistence of activity within the AKT pathway and truncation and dimerisation of BRAF V600E.[6,7]

Summary of primary pharmacology

The primary pharmacology studies indicate inhibition of BRAF V600 mutant kinase activity and subsequent reduction in signalling through ERK and MEK resulting in a reduction in melanoma cell proliferation, and tumour regression and increased life span in a mouse model bearing a melanoma xenograft. The efficacious doses/concentrations were below that anticipated clinically, thus supporting the proposed clinical use. Resistance developed relatively quickly both *in vitro* and *in vivo* and is considered possible during clinical use. While vemurafenib inhibited wild-type BRAF kinase activity with similar potency, the downstream signalling effects were markedly different from those of the mutant, with vemurafenib having no effect on the proliferation of cells harbouring wild-type BRAF kinase.

Secondary pharmacodynamics

Activity against other kinases

Vemurafenib was assessed in *in vitro* assays for inhibitory activity against a wide range of kinases. Significant activity was seen against CRAF, ARAF, SRMS, ACK1, MAP4K5 and FGR with IC_{50} values (16–63 nM) less than the clinical free plasma C_{max}. Inhibitory activity was also seen at BRK, LCK, NEK11 (IC_{50} for each 1.3 to 2 times the clinical free plasma C_{max}), FYN, KIT, BLK, LYNB, KDR, YES1, WNK3, STK3 and LYNA (IC_{50} values for each 3 to 6 times the peak free plasma concentration). While inhibition of these kinases occurred at clinically relevant concentrations, the *in vivo* downstream effects cannot be predicted due to the complexity of the downstream signalling pathways

Activity against cutaneous squamous cell carcinoma (cuSCC)

Enhanced tumour growth and a decrease in lifespan were seen in mice bearing human cuSCC xenografts expressing wild-type BRAF treated with 75 mg/kg PO bd vemurafenib for 14 days (exposure based on AUC [exposure ratio $(ER)_{AUC}$] 0.5). These data suggest that vemurafenib may promote the growth of pre existing cuSCC lesions at the proposed clinical dose. Vemurafenib had no significant effect on MAPK or MEK1 phosphorylation in these cells, suggesting tumour growth promotion was not due to enhanced signalling through MAPK and MEK1.

[6] Atefi, M., E. Von Euw, N. Attar, C. Ng, C. Chu, D. Guo, R. Nazarian, B. Chmielowski, J.A. Glaspy, B. Comin-Anduix, P.S. Mischel, R.S. Lo and A. Ribas. (2011) Reversing melanoma cross-resistance to BRAF and MEK inhibitors by co-targeting the AKT/mTOR pathway. *PLOS One* **6:** e28973.

[7] Molina-Arcas, M. And J. Downward. (2012) How to fool a wonder drug: truncate and dimerize. *Cancer Cell* **21:** 7-9.

Activity against other targets

In a screen of 63 receptors, transporters, ion channels and enzymes, vemurafenib had no significant inhibitory activity at concentrations ≤10 μM (~60 times the clinical free plasma C_{max}). Aside from activity on other kinases, no other off-target activities are predicted.

Safety pharmacology

Specialised safety pharmacology studies covered the central nervous system (CNS), cardiovascular and respiratory systems. All studies were Good Laboratory Practice (GLP) compliant. However, the *in vivo* studies are difficult to interpret as there were no accompanying plasma kinetic data. The crystalline form of vemurafenib was used and considerable difference in bioavailability was seen with different crystalline forms and different vehicles and therefore direct comparison with the clinical exposure cannot be definitively made. Plasma kinetic data from single dose pharmacokinetic studies which used the same vehicle and used the crystalline form of vemurafenib (albeit different drug lots) (Report 1041532 for rats and Report 1041531 for dogs[8]) were used broadly for comparative purposes.

In specialised safety pharmacology studies, CNS and respiratory function were unaffected in rats treated with 1000 mg/kg PO. However, plasma levels are estimated to be subclinical in these studies and thus, little weight can be placed on the negative findings. There were no clinical signs of CNS toxicity or respiratory depression in repeat-dose toxicity studies in rats and dogs but again plasma levels of vemurafenib were similar to or below clinical plasma levels. Therefore, the submitted animal studies are not adequate to predict potential adverse CNS or respiratory effects.

In vitro, vemurafenib showed a concentration dependent inhibition of the hERG potassium (K^+) channel. Though concentrations used in *in vitro* assays are difficult to extrapolate safety margins for clinical use, a 30 fold difference between unbound drug concentrations at the C_{max} and the hERG K^+ IC_{50} is generally considered a "safe" margin.[9] The IC_{50} of 1.25 μM is 7.5 times the peak free level in patients and therefore an adequate safety margin has not been demonstrated and the results identify potential hazards to the cardiovascular system. Longer QTc intervals were seen in two dogs treated with 1000 mg/kg PO vemurafenib in the specialised cardiovascular study and in male dogs treated with 150 mg/kg PO bd in a 13 week repeat dose toxicity study. The C_{max} values in these studies were below the clinical C_{max}. No consistent effects were seen on action potential duration in dog Purkinje fibres. However, there were technical errors in this study, such that only two fibres were exposed to drug at a single concentration (~7.6 μM). The small sample size and single tested concentration limits the interpretation of results from this study. Nonetheless, a definite decrease in maximum rate of rise of the membrane voltage during an action potential (Vmax) was seen, suggesting the potential for conduction delay. Overall, the data indicate the potential for QT interval prolongation[10] and conduction delay during clinical use.

[8] Report 1041532: the C_{max} in rats that received 1000 mg/kg PO vemurafenib in corn oil was 18 μg/mL; Report 1041531: the C_{max} in dogs that received 1000 mg/kg PO vemurafenib in corn oil was 6.3 μg/mL

[9] Redfern, W.S., L. Carlsson, A.S. Davis, W.G. Lynch, I. MacKenzie, S. Palethorpe, P.K.S. Siegl, I. Strang, A.T. Sullivan, R. Wallis, A.J. Camm and T.G. Hammond. (2003) Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. *Cardiovascular Res.* **58:**32-45.

[10] QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death.

Pharmacokinetics

An *in vitro* study indicated vemurafenib had low cell permeability and oral absorption was limited by its low aqueous solubility. Poor oral bioavailability was seen with early formulations used in animal studies resulting in low and variable exposure. Various formulations were evaluated to increase exposure. The MBP formulation was selected to achieve higher systemic exposures. The rate of absorption following oral administration of the MBP formulation of vemurafenib was similar across animal species and human subjects (2–8 h). Studies in dogs indicated the upper gastrointestinal tract was the major site of absorption. Absorption appeared to be saturable in rats and dogs at doses used in the toxicity studies. The elimination half-life was short in rats and dogs (1.5–3.5 h) and much longer in rabbits and humans (15–34 h). Following IV administration, clearance was low in animals and similar across species. Exposures in female rats were generally 2–5 times higher than in their male counterparts, which was probably associated with greater metabolism in males than females. There was no apparent sex difference in dogs.

Plasma protein binding by vemurafenib was high and independent of concentration in mouse, rat, dog, monkey and human plasma and comparable across species (99.8–99.9%). The high protein binding in human plasma was mainly attributed to albumin and α_1-acid glycoprotein. The volume of distribution was similar to total body water in all species and following administration of radioactive carbon labelled (^{14}C) vemurafenib to pigmented rats, radioactivity was widely distributed with tissue concentrations having similar levels of radioactivity as those in blood, with the exception of organs involved in excretion, which had much higher levels of radioactivity. There was no evidence of blood-brain barrier penetration and there was no specific affinity or retention in melanin-containing tissues.

Metabolism of vemurafenib was generally low in all species and involved hydroxylation, oxidation and glucuronidation. Another metabolite detected in the faeces and urine of humans but not in rat or dog samples was tentatively identified as a glucosylated metabolite. *In vitro* studies indicated a major role of cytochrome P450 (CYP) isozyme 3A4 in the formation of the monohydroxylated metabolites. The enzymes involved in the formation of the conjugated metabolites were not identified. Unchanged drug was the most dominant species in the plasma of female rats, dogs and humans (>90% of drug-related material). Unchanged drug was also the predominant species in the plasma of male rats 1–12 h post dose; however monohydroxylated metabolites were the main drug-related material 12–24 h post dose, indicating greater metabolism of vemurafenib in male rats compared to female rats, probably contributing to the sex differences in vemurafenib exposure seen. All circulating metabolites in human plasma were also seen in the plasma of rats and dogs, the species used in the toxicity studies.

Excretion of drug-related material was predominantly in the faeces in rats and humans. A comparison of excretion in rats following oral and intravenous (IV) administration indicated high faecal excretion of unchanged drug following oral administration, probably as a result of unabsorbed material and high biliary excretion almost exclusively of oxidative metabolites following IV administration. In humans, drug-related material consisted primarily of unchanged drug, possibly also as a result of unabsorbed drug, with minor contributions of a monohydroxylated metabolite, a glucuronide metabolite and the putative glucosylated metabolite. Based on both *in vitro* and *in vivo* studies, the latter metabolite was not detected in rats or dogs. With the exception of this metabolite, the pharmacokinetic profile of vemurafenib was qualitatively similar in humans, rats and dogs, thus supporting the use of the latter animal species in toxicity studies.

Pharmacokinetic drug interactions

Only minor metabolism of vemurafenib occurs and this drug was only a weak substrate of P-glycoprotein, therefore, co-administered drugs that are CYP450 or P-glycoprotein inhibitors/inducers are unlikely to alter the plasma kinetics of vemurafenib. At ≥1 μM, there was a concentration-dependent induction of pregnane X receptor (PXR), which is involved in CYP3A4 induction and an induction of CYP3A4 mRNA levels was seen in human hepatocytes; however, there was no increase in CYP3A4 enzyme activity at concentrations up to 10 μM.

There was no significant induction of CYP1A2, 2B6 or 2C9 messenger ribonucleic acid (mRNA) levels and/or enzyme activity at concentrations up to 10 μM and no significant inhibition of CYP2A6 and 2E1 activity at concentrations ≤50 μM. Vemurafenib (at 10 μM) was not a substrate of the human hepatic transporters, OATP1B1 or OATP1B3 and no inhibition of these transporters was seen at concentrations up to 50 μM. The clinical relevance of the negative findings is difficult to interpret as the tested concentrations were below or well below clinical plasma levels (trough plasma concentration (C_{trough}) 119 μM [58.5 μg/mL]).

Vemurafenib inhibited CYP1A2 (IC_{50} 33 μM), 2C9 (IC_{50} 4.3–5.9 μM), 2C19 (IC_{50} 4.1 μM), CYP2D6 (IC_{50} 33 μM) and 3A4 (IC_{50} 13–14 μM) activity in human liver microsomes and/or recombinantly expressed enzymes. There was no indication of time-dependent inactivation of CYP3A4/5 in human liver microsomes at 10 μM, suggesting vemurafenib is not an irreversible inhibitor of CYP3A4. Inhibition of P-glycoprotein was also seen (IC_{50} 3.5–17 μM). As the IC_{50} values are below clinical plasma levels (C_{trough} 119 μM), these findings are assumed to be clinically-relevant.

Toxicology

General toxicity

Acute toxicity

No adequate single dose toxicity studies were submitted. A number of single dose tolerability studies were submitted which did not meet the European Union (EU) guideline for single dose toxicity. While more than one species was used, only males were assessed and only one route of administration was tested (the clinical route, PO) except for a single experiment in rats using IV administration. IV administration resulted in the immediate deaths of all animals and these were attributed by the sponsor to the vehicle used (dimethyl sulfoxide (DMSO), Labrosol and water) and no further investigation of effects of vemurafenib by this route was conducted. The observation period in these studies was too short, one day in all cases rather than 14 days and necropsies were performed only in one study on rats. While no mortalities were seen in mice up to 300 mg/kg PO, rats and dogs (both up to 1000 mg/kg PO), maximum exposures achieved were below the anticipated clinical exposure; 0.75 times the clinical $AUC_{0\text{-}24h}$ in mice, 0.64 times in rats and 0.15 times in dogs. Furthermore, the exceptionally short observation period (24 h rather than 14 days) indicates that any delayed toxicity would not have been seen in these studies. This, combined with the lack of post mortem analyses in all but one of the studies means these studies provide no useful information on the acute toxicity profile of vemurafenib.

Repeat dose toxicity

GLP compliant repeat dose toxicity studies by the oral route were conducted in rats (up to 26 weeks) and dogs (up to 13 weeks). A number of additional short term, non-GLP toxicity studies in mice, rats and dogs were submitted. These studies had limited reporting, were of short duration and exposures achieved were lower than those in the longer GLP studies

and so findings from these studies are not discussed below. The choice of species (rat as the rodent and dog as the non-rodent species), the duration of pivotal studies, group sizes and the use of both sexes were consistent with TGA adopted EU guidelines. Dosing in the rat studies and some of the dog studies was once daily. Greater toxicity was seen when twice daily dosing was used in dogs with overall comparable systemic exposure seen between once daily and twice daily dosing at the same daily dose. The studies in dogs with twice daily dosing are the most relevant as this is the intended dose regimen.

A 39 week study with twice daily dosing to dogs was terminated prematurely (after 37 days) due to poor tolerability. The pivotal 13 week study with twice daily dosing used animals from this previous study, which could confound the results of the study. The MBP formulation was used in the longer term studies in rats and dogs. The maximum doses used in the 26 week study in rats and the 13 week once daily dosing to dogs was stated to be the maximum feasible in the MBP formulation. The maximum dose in the pivotal 13 week study in dogs was chosen to be lower than the doses that were poorly tolerated in the prematurely terminated study. High dose animals in this study lost bodyweight, indicating the maximum tolerated dose was assessed. Maximum exposures in rats were similar to the anticipated clinical exposure (Table 2) while systemic exposures in all of the dog studies were subclinical. Therefore, the full toxicological profile of vemurafenib is unlikely to have been revealed in the submitted studies. Due to the generally subclinical exposures in the toxicity studies, all of the findings described below must be assumed to be clinically-relevant.

Hepatic toxicity

Increased liver enzymes[11] were seen in dogs treated with vemurafenib. Only sporadic elevations were seen in dogs treated once daily at 450 mg/kg/day PO, while significant and persistent elevations were seen following twice daily dosing at ≥75 mg/kg PO bd (ER_{AUC} 0.3). The elevated enzyme levels were accompanied by microscopic changes in the liver (necrosis and individual hepatocellular degeneration, the presence of pigment in hepatocytes and Kupffer cells, perivascular mixed infiltrates and an increase in the number of Kupffer cells in the liver). Secretions were also seen in the gall bladder. With the exception of minimal perivascular mixed infiltrates and the presence of minimal amounts of pigment in hepatocytes and Kupffer cells, all of the hepatic changes had reversed after a 4 week treatment-free period. Elevated levels of serum cholesterol were consistently seen in both rats and dogs, across multiple studies. Based on a consistency of this finding across species and across studies at or below the clinical exposure, elevated serum cholesterol levels may be expected to occur in patients. Altogether these findings indicate hepatic toxicity is likely during clinical use.

[11]ALT=alanine aminotransferase; AST=aspartate aminotransferase; ALP=alkaline phosphatase and GGT=gamma glutamyltransferase

Table 2. Relative exposure to vemurafenib in selected repeat-dose toxicity studies

Species strain	Report	Treatment duration	Dose mg/kg/day PO	AUC_{0-24h} µg·h/mL	C_{max} µg/mL	Exposure ratio based on	
						AUC	C_{max}
Rat (SD) (♂/♀)	1040820	4 weeks	30	119/189	10/19	0.11/0.17	0.17/0.31
			100	256/388	21/30	0.23/0.34	0.34/0.49
			1000	1228/855	76/81	1.1/0.76	1.2/1.3
	1025760	26 weeks	10	32/62	5.3/9.0	0.03/0.06	0.09/0.15
			50	59/236	15/32	0.05/0.21	0.24/0.52
			450	595/1577	68/132	0.53/1.4	1.1/2.1
Dog (Beagle)	1040819	4 weeks	30	57	7.3	0.05	0.12
			100	96	12	0.09	0.20
			1000	223	21	0.20	0.34
	1025759	13 weeks	30	46	7.0	0.04	0.11
			150	201	25	0.18	0.41
			450	355	38	0.32	0.62
	1032862	13 weeks	75 bid	329	25	0.30	0.41
			150 bid	468	36	0.42	0.59
	1033163	37 days	50 bid	199	17	0.18	0.28
			150 bid	481	37	0.43	0.60
			300 bid	585	48	0.52	0.78
			450 bid	634	45	0.56	0.73
Human	NP25163	steady state	960 mg bid	1126	61.4	–	–

Gastrointestinal effects

Vomiting and diarrhoea were seen in all of the dog studies. Exposures in all studies were subclinical. Discoloured (sometimes green), white and/or liquid faeces were seen in all groups, including those receiving the placebo blend (containing the excipient polymer hydroxypropyl methylcellulose acetate succinate), suggesting some contribution of the polymer to the loose faeces. Mucoid faeces were only seen in treated animals. These clinical signs were more severe following twice daily rather than once daily dosing. The vomiting and diarrhoea resulted in significant deterioration of body condition in dogs treated with ≥150 mg/kg PO bd vemurafenib. Dogs treated twice daily with vemurafenib (≥75 mg/kg PO bd) appeared to have abdominal pain, as evidenced by vocalisation during handling or abdominal palpation. Duodenal discolouration was seen in one animal treated with 450 mg/kg bd PO for 10 days. Vomiting and diarrhoea resolved quickly (within 1 week) and the bodyweight condition of dogs was restored after cessation of treatment. No consistent gastrointestinal findings were seen in rats. Minimal to moderate intestinal lymphangiectasis in the jejunum, consistent with dilatation of lacteals in the lamina propria, were seen in rats treated with ≥100 mg/kg/day PO vemurafenib for 4 weeks

(ER_{AUC} 0.23–0.34). This was only partially reversible following a 14 day treatment free period. No significant gastrointestinal tract findings were seen in rats treated for longer at higher exposures in another study. Overall, the studies indicate vomiting, diarrhoea and abdominal pain may be seen in patients taking vemurafenib.

Bone marrow toxicity

Bone marrow necrosis was observed in the sternum of one dog treated with 450 mg/kg PO bd for 10 days in the prematurely terminated 39 week repeat-dose toxicity study. The possibility that vemurafenib was directly cytotoxic to bone marrow was investigated *in vitro* in human, dog and rat cells. Partial cytotoxicity was seen on two haematopoietic cell lineages (granulocyte-macrophage colony forming cells and megakaryocyte colony forming cells) from all species at ≥15.6 μM[12] (IC_{50} 150–190 μM in dogs). No consistent haematology changes were seen in the toxicity studies. Reduced neutrophils were seen in female rats treated with 450 mg/kg/day PO vemurafenib for 26 weeks (ER_{AUC} 1.4) while increased levels of white blood cells (neutrophils, lymphocytes and eosinophils) were seen in dogs treated with 150 mg/kg PO bd vemurafenib for 13 weeks (ER_{AUC} 0.42). The pattern in dogs is similar to that of an allergic reaction. There were no significant bone marrow changes in these studies. The absence of consistent haematology and bone marrow effects in the animal studies are difficult to interpret due to the generally subclinical exposures achieved. As inhibition of haematopoetic cells was seen *in vitro* at clinically relevant concentrations and human cells appeared to be more sensitive, some haematological changes (such as neutropaenia or basopaenia) may be seen clinically.

Genotoxicity and carcinogenicity

The potential genotoxicity of vemurafenib was investigated in the standard battery of tests, conducted in accordance with TGA adopted EU guidelines. All assays were appropriately validated and conducted under GLP conditions. Appropriate bacterial strains were used in the Ames test and concentrations used in the *in vitro* assays were appropriate. The highest dose in the rat micronucleus study (800 mg/kg PO) is estimated to result in an exposure similar to that seen clinically[13], and was stated to be the maximum feasible dose in the MBP formulation. Higher exposures may have been achievable with twice daily dosing. Vemurafenib was not mutagenic in bacterial mutation assays or clastogenic *in vitro* (in human lymphocytes) or *in vivo* (in the rat micronucleus test).

No carcinogenicity studies were conducted, which is considered acceptable given the target patient group.[4]

Reproductive toxicity

The only reproductive toxicity studies submitted were embryofetal development studies in the rat and the rabbit. No studies on fertility or post natal development were submitted, which is considered acceptable given the intended patient group (ICH S9). In the pivotal embryofetal development studies, adequate animal numbers were used and treatment periods were appropriate. Maximum exposures achieved in the pivotal studies were at or below the anticipated clinical exposure (Table 3). Based on the dose-ranging studies, higher exposures would have been achievable in rats, while the reduced bodyweight gain and food consumption at the highest dose in rabbits, suggests this dose was the maximum tolerated.

[12] The units were not clear in the report as μg/mL and μM appeared to be used interchangeably. For the purposes of this Assessment, the units were assumed to be μM.

[13] Based on data in Study 1041430, where an 800 mg/kg PO dose of the MBP formulation of vemurafenib resulted in an $AUC_{0\text{-}24h}$ of 1130 μg.h/mL.

Vemurafenib crossed the placenta in rats and rabbits with fetal levels 4 h post dose 1.8–5.8% of the maternal levels. Fetal exposure appeared to increase in a dose-related manner. In the rat embryofetal development study, a number of fetal anomalies (vertebral agenesis, right-sided aortic arch and lobular dysgenesis of the lungs) were seen only at the high dose. There were only single incidences of these anomalies and in the case of vertebral agenesis and lobular dysgenesis of the lungs, the incidences were within historical controls. The visceral malformation, right-sided aortic arch, is a rare malformation not previously seen in a historical control database of ~40 000 fetuses. As this malformation occurred in the high dose group and the incidence was outside the historical control, an association with treatment cannot be dismissed. There were no adverse effects seen on embryofetal development in rabbits; however, exposures in these studies were well below the anticipated clinical exposure and little weight can be placed on the predictive value of the negative findings. As vemurafenib crossed the placenta, with a potentially drug-related malformation seen in an exposed fetus at clinical plasma levels and pharmacologically vemurafenib inhibits multiple kinases (including BRAF) that may be important during embryofetal development, placement in Pregnancy Category D seems appropriate.

Table 3. Relative exposure to vemurafenib in reproductive embryofetal toxicity studies

Report	Species & strain	Dose (mg/kg/day); PO	AUC_{0-24h} (µg·h/mL)	Exposure ratio (animal:human AUC_{0-24h})
1026029 *[dose-ranging]*	**Rat** (SD)	30	231	0.21
		150	625	0.56
		800	2400	2.1
1028543 *[main study]*	**Rat** (SD)	30	160	0.14
		100	408	0.36
		250	1590	1.4
1026033 *[dose-ranging]*	**Rabbit** (NZW)	30	148	0.13
		150	375	0.33
		450	605	0.54
1028544 *[main study]*	**Rabbit** (NZW)	30	128	0.11
		150	386	0.34
		450	508	0.45
NP25163	**Human**	[960 mg bid; steady state]	1126	–

Phototoxicity

Vemurafenib absorbs ultraviolet (UV) light between 240 nm and 450 nm and was shown to be phototoxic *in vitro* to cultured cells (IC_{50} 0.197 µg/mL). There was no evidence of dermal erythema or any other skin reactions in female hairless rats treated with ≤450 mg/kg PO vemurafenib. However, based on the low exposures in the *in vivo* study

(estimated maximum AUC 0.65 times the anticipated clinical exposure[14]), little weight can be placed on the negative findings. As vemurafenib was phototoxic *in vitro* and did distribute to the skin in the tissue distribution study, phototoxic reactions on sun-exposed skin must be assumed to be possible during clinical use.

Impurities

Six impurities in the drug substance were specified at limits above the EU guideline qualification threshold (0.05% for a drug with a daily dose of 1920 mg). Four of these impurities were considered qualified at the proposed limits by the submitted data. The remaining two impurities were not considered qualified at the proposed limits. This has been referred to the quality evaluator.

Nonclinical summary and conclusions

Summary

- The submitted nonclinical data were in general accordance with the relevant guideline on the nonclinical evaluation of anticancer pharmaceuticals.[4] All pivotal pharmacology, repeat-dose toxicity and reproductive toxicity studies were conducted using the clinical MBP formulation. In general, the exposures to vemurafenib were subclinical in the animal studies and therefore the full spectrum of safety issues has not been adequately addressed in the submitted data. This is considered a major limitation but for the most part was unavoidable as the maximum feasible dose was used in the majority of the pivotal toxicity studies.

- Vemurafenib inhibited BRAF V600 mutant (V600D, V600E, V600K and V600R) kinase activity with a subsequent reduction in signalling through ERK and MEK resulting in inhibition of melanoma cell proliferation. Tumour regression and increased life span were seen in a mouse model bearing a human melanoma xenograft. The efficacious doses/concentrations were below that anticipated clinically, thus supporting the proposed clinical use. Resistance developed relatively quickly both *in vitro* and *in vivo* and is considered possible during clinical use.

- Vemurafenib had significant inhibitory activity at 18 other kinases including wild-type BRAF, CRAF and ARAF at clinically-relevant concentrations. There was no significant inhibitory activity on 63 receptors, transporters, ion channels and enzymes at concentrations ≤10 μM. Aside from activity on other kinases, no other off-target activities are predicted.

- Vemurafenib accelerated the growth of cutaneous squamous cell carcinoma (cuSCC) cell lines both *in vitro* and in animal xenograft models. This occurred at clinically relevant concentrations suggesting that vemurafenib may promote the growth of pre existing cuSCC lesions at the proposed clinical dose.

- Safety pharmacology studies covered the CNS, cardiovascular and respiratory systems. CNS and respiratory function were unaffected in rats treated with 1000 mg/kg PO. However, plasma levels are estimated to be subclinical in these studies and thus, little weight can be placed on the negative findings. *In vitro*, vemurafenib inhibited the hERG K^+ channel at clinically relevant concentrations. There were occasional incidences of

[14] Based on Day 1 data in Report 1025760 where an $AUC_{0\text{-}24h}$ of 732 μg•h/mL was seen in female rats that received 450 mg/kg PO vemurafenib in the MBP formulation.

longer QTc intervals in dogs treated with vemurafenib. The data indicate the potential for QT prolongation during clinical use.

- Pharmacokinetic studies indicated oral absorption of vemurafenib was to some extent rate limited at high doses presumably due to its poor solubility. The volume of distribution in mice, rats, dogs and monkeys was moderate and tissue distribution wide in rats. Vemurafenib was highly protein bound in the plasma from animals and humans. Metabolism of vemurafenib was limited, with CYP3A4 primarily involved in the formation of small amounts of monohydroxylated metabolites. Excretion appears to be almost exclusively via the biliary route as indicated in mass balance studies.

- Based on *in vitro* studies, vemurafenib (at clinical plasma concentrations) has the potential to increase the exposure of co-administered drugs that are substrates of CYP1A2, 2C9, 2C19 and 2D6 and P-glycoprotein, and decrease the exposure of co-administered drugs that are CYP3A4 substrates. Only minor metabolism of vemurafenib occurs and this drug was only a weak substrate of P-glycoprotein, therefore, co-administered drugs that are CYP450 or P-glycoprotein inhibitors/inducers are unlikely to alter the plasma kinetics of vemurafenib.

- Repeat dose toxicity studies by the oral route were conducted in rats (up to 26 weeks) and dogs (up to 13 weeks). The highest doses were the maximum feasible (in rats) or the maximum tolerated (in the pivotal dog study). However, the maximum exposures in rats were similar to the anticipated clinical exposure while systemic exposures in all of the dog studies were subclinical. Therefore, the full toxicological profile of vemurafenib is unlikely to have been revealed in the submitted studies. The findings of clinical relevance seen almost exclusively in the dog studies include: reversible dose-dependent increases in serum liver enzymes[15], cholesterol, and/or triglycerides. The increases in liver enzymes were accompanied by necrosis and individual hepatocellular degeneration. Vomiting, diarrhoea and clinical signs of abdominal pain were also seen. Bone marrow necrosis was observed in the sternum of one dog treated with 450 mg/kg PO bd for 10 days. *In vitro* studies indicated vemurafenib was partially cytotoxic to haematopoietic cells at clinically relevant concentrations.

- No signs of genotoxicity were observed in three standard *in vitro* tests or in one *in vivo* assay following single oral doses up to 800 mg/kg. No studies on carcinogenicity were submitted, which is considered acceptable.

- Studies on reproductive toxicity were limited to embryofetal developmental studies conducted in rats and rabbits. Maximum exposures achieved in the pivotal studies were at or below the anticipated clinical exposure. Vemurafenib crossed the placenta in rats and rabbits with fetal levels 1.8 to 5.8% maternal levels. In the rat embryofetal development toxicity study, there was a single incidence of a rare malformation that could potentially be related to vemurafenib treatment. There were no adverse effects seen on embryofetal development in rabbits; however, exposures in these studies were well below the anticipated clinical exposure and little weight can be placed on the predictive value of the negative findings.

- Vemurafenib absorbs UV light significantly between 240 nm and 450 nm, was phototoxic in fibroblasts *in vitro* and distributed to the skin in the tissue distribution

[15] GGT=gamma glutamyltransferase; ALP= serum alkaline phosphatase; ALT= alanine aminotransferase and AST=aspartate aminotransferase

study. Therefore, phototoxic reactions on sun exposed skin must be assumed to be possible during clinical use.

- Four impurities in the drug substance were considered qualified at the proposed limits by the submitted data. Two impurities were not considered qualified.

Conclusions and recommendations

The primary pharmacology studies are supportive of the proposed use of the drug as an oral agent for the treatment of patients with melanoma which is positive for BRAF V600 mutations.

However, the full toxicological profile of vemurafenib is unlikely to have been revealed in the submitted studies, as the animal exposures were, for the most part, subclinical. Notable findings of clinical relevance include:

- Potentiation of pre-existing cuSCC lesions;
- QT prolongation;
- Hepatotoxicity;
- Gastrointestinal disturbances;
- Photo-reactions on the skin

Due to the deficiencies in the nonclinical data, a recommendation for registration will need to rely on an acceptable benefit/risk profile based on clinical data.

Amendments to the PI were also recommended but these are beyond the scope of this AusPAR.

IV. Clinical findings

Introduction

The clinical data included data on one biopharmaceutic study (PLX102-01) to assess the relative bioavailability of VEM in two formulations versus a reference Phase I formulation.

Human pharmacokinetics (PK) studies including PLX06-02, which is a dose escalation study to evaluate the safety and PK of VEM in patients with solid tumours, with subsequent extension to evaluate objective tumour response, progression free survival and overall survival in patients with BRAF V600E+ metastatic melanoma or colorectal cancer.

The second study was NP25158 in which the primary objective was to assess the mass balance routes and rates of elimination of carbon14 labelled VEM. Study NP25163 had a primary objective to evaluate the pharmacokinetics of VEM using the 240 mg MBP tablet formulation. Study NP22676 primary objective is to investigate the effect of VEM on the pharmacokinetics of each substance in a combination of five product drugs for CYP450 dependent metabolism.

There were no human pharmacodynamic (PD) studies performed in this submission.

The pivotal efficacy and safety Study NO25026, which was to evaluate the efficacy of VEM as a monotherapy compared to dacarbazine in terms of progression free survival (PFS) and overall survival (OS) in previously untreated patients with $BRAF^{V600}$ mutation positive metastatic melanoma.

The supportive study submitted was Study NP22657, whose primary objective was to evaluate the efficacy of VEM in previously treated patients with $BRAF^{V600}$ mutation positive metastatic melanoma by best overall response rate as assessed by an independent review committee (IRC) using Response Evaluation Criteria in Solid Tumours (RECIST)[16] criteria (version 1.1) for metastatic melanoma.

All aspects of good clinical practice were observed in these studies.

Pharmacokinetics

Studies providing pharmacokinetic data:

The clinical pharmacokinetics of VEM provided in this submission were characterised using the non-compartmental analysis (NCA) of pharmacokinetic data from seven clinical studies, including five Phase I Studies PLX06-02, PLX102-01, NP22676, NP25163 and NP25158; one Phase II Study NP22657 and one Phase III Study NO25026. In addition VEM plasma concentration data from NP25163, NP22657 and NO25026 were utilised to develop a population pharmacokinetic model. The population PK model was used to describe the pharmacokinetics of VEM and to investigate the potential influence of co-variates that contribute significantly to the between-patient variability in pharmacokinetic parameters of VEM and to characterise the exposures/efficacy and exposure/safety relationships for select efficacy and safety endpoints (population PK/PD).

Summary of pharmacokinetics:

The initial Phase I Study PLX06-02 was conducted using the original VEM crystalline formulation and evaluated doses up to 1600 mg twice daily. Subsequently the MBP formulation of VEM was developed and evaluated in a single dose three-way crossover study in healthy volunteers. The MBP formulation was introduced into PLX06-02 at 160 mg twice daily.

During the dose escalation phase of the Phase I of the PLX06-02, several different capsule strengths and formulation processes of the optimised MBP formulation were introduced to evaluate dosages ranging from 160 mg to 1120 mg twice daily. A 40 mg capsule (dry granulation) was used to evaluate exposure doses of 160, 240 and 360 mg twice daily and an 80 mg capsule (wet granulation) was used to allow further dose escalation in the 720 and 1120 mg twice daily cohort. A 120 mg capsule (dry granulation roller compaction) was introduced to evaluate the 960 mg twice daily regimen during dose escalation and the melanoma and colorectal cancer (CRC) extension cohort. The results of the dose escalation phase of PLX06-02 was the optimised MBP formulation (capsule formulation) showed that the steady state exposure levels (C_{max}, $AUC_{0\text{-}8\ h}$ and $AUC_{0\text{-}24\ hours}$) increased with escalating doses.

Based on the DLTs reported at the 1120 mg twice daily level, the 960 mg twice daily doses were selected for use in all subsequent studies.

The MBP capsule formulations used in PLX06-02 were then replaced with the proposed commercial formulation a 240 mg film coated tablet and were administered at the recommended dose of 960 mg twice daily in all subsequent studies including the melanoma extension cohort of PLX06-02, and the various Phase II and Phase III studies.

[16] Response Evaluation Criteria In Solid Tumors (RECIST) is a set of published rules that define when cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progression") during treatments established by an international collaboration including the European Organisation for Research and Treatment of Cancer (EORTC), National Cancer Institute of the United States, and the National Cancer Institute of Canada Clinical Trials Group.

Only one single dose three-way crossover relative bioavailability study was conducted in healthy subjects (Study PLX102-01) prior to the identification of the risk for developing cutaneous squamous cell carcinoma (cuSCC). Because of this, no further pharmacokinetic studies in healthy subjects were possible. Furthermore inability to obtain multiple serial PK sampling in melanoma patients and the use of a twice daily dosing paradigm limited the robust characterisation of the elimination half-life, apparent clearance (CL-F) as volume of distribution (D-F) by NCA.

Summary results of individual studies:

Study PLX06-02:

This was the first human Phase I dose escalation study that evaluated the safety and PK of VEM in patients with solid tumours and determined the MTD. The study involved 12 investigators and seven centres, five in the US and two in Australia. The primary objective of the dose escalation phase of the study was to evaluate the safety and PK of VEM in patients with solid tumours.

A treatment extension cohort was also undertaken to evaluate the objective tumour response including overall response rate, duration of response and progression free survival and overall survival as well as PK of VEM in patients with $BRAF^{V600E+}$ metastatic melanoma or CRC.

Inclusion criteria for the study included male or female patients of at least 18 years with solid tumours confirmed histologically, whose tumours were refractory to standard therapy. Patients from whom paired biopsies were planned must have a V600E+ BRAF mutation confirmed. Patients in the extension phase study required measurable disease by RECIST criteria, an ECOG performance status[17] of 0 or 1 and a life expectancy of at least three months with normal haematologic and biochemical parameters.

In the dose escalation phase of the study patients received VEM administered on Days 1-29 or longer in the fasted state. Cohorts of 3-6 patients were assigned to ascending doses twice daily of the original formulation. After PK assessment on day 15 adequate safety and tolerability were shown on Day 28, the next cohort of 3-6 patients were enrolled with a 50-100% increase in VEM dose. The differences in VEM dose treatment of the various formulations used in the study, the actual percentage increase of VEM dose varied from one cohort to the next. The dose escalation phase of study continued until a maximum dose was defined. Each patient in the dose escalation phase received the assigned VEM dose of four weeks. Afterwards patients were offered continued dosing with VEM based on tolerability and absence of disease progression.

[17] ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

0 - Fully active, able to carry on all pre-disease performance without restriction

1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

5 – Dead

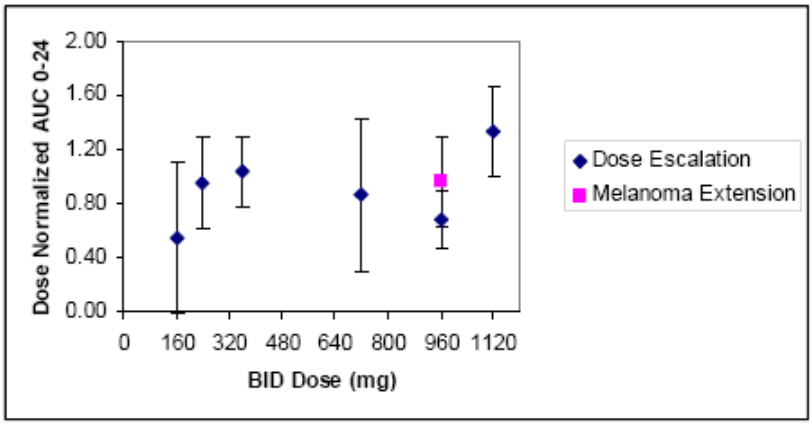
In the treatment extension phase, once the maximum tolerated dose of VEM was selected based on the PK and safety results of the dose escalation phase, patients with $BRAF^{V600E+}$ metastatic melanoma or CRC were enrolled in two respective treatment PK extension cohorts, each of which was planned to enrol 20-26 patients in parallel. The patients in the extension cohorts received treatment until disease progression, death or withdrawal from the study.

Pharmacokinetic parameters assessed included area under the plasma concentration time curve over a dosing interval ($AUC_{0\text{-}t}$) and area under the plasma concentration time curve from time zero to infinity ($AUC_{0\text{-}infinity}$), PK concentration (C_{max}), time to PK concentrations (T_{max}), half-life ($T_{1/2}$) and terminal elimination rate constant (K_{el}).[18] The PK parameters were estimated by non-compartmental PK analysis (NCA) of the plasma VEM concentration time course curve for each patient in the PK population. PK parameters were summarised using descriptive statistics.

Results of PK analyses revealed the mean dose normalised values for VEM AUC and C_{max} appeared to be dose proportional between 240 and 960 mg twice daily and greater than dose proportional for 1120 mg twice daily, which is also the dose at which DLTs were observed and indicated in Figures 4 and 5. Thus, 960 mg twice daily was selected for the MTD and the recommended dose for further evaluation in the melanoma and CRC extension cohorts.

Figure 4.

PLX06-02: Relationship of Mean RO5185426 Dose Normalized $AUC_{0\text{-}24h}$ (± SD) with Dose on Day 15 – MBP Dose Escalation and Melanoma Extension Cohorts

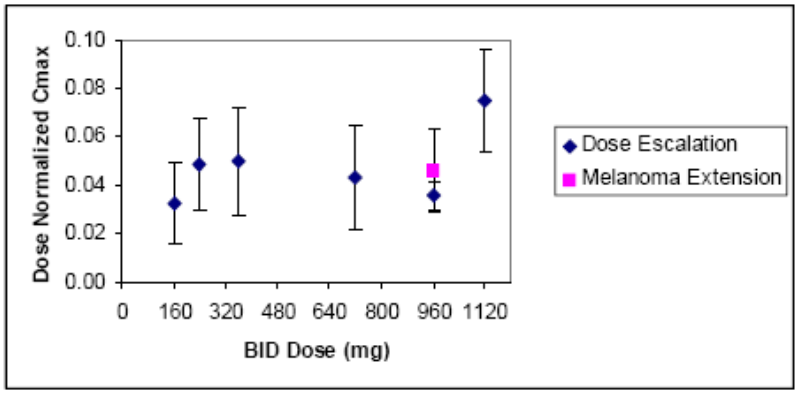


Note: The 3 patients who received 960 mg RO5185426 bid during the dose escalation phase are included in the melanoma extension cohort.

[18] Sponsor comment: "While these PK parameters were planned to be assessed, because of the flat concentration-time profile at Day 15 and the limited PK sampling, the elimination half-life could not be derived with confidence in this study."

Figure 5.

PLX06-02: Relationship of Mean RO5185426 Dose Normalized C_{max} (± SD) with Dose on Day 15 – MBP Dose Escalation and Melanoma Extension Cohorts

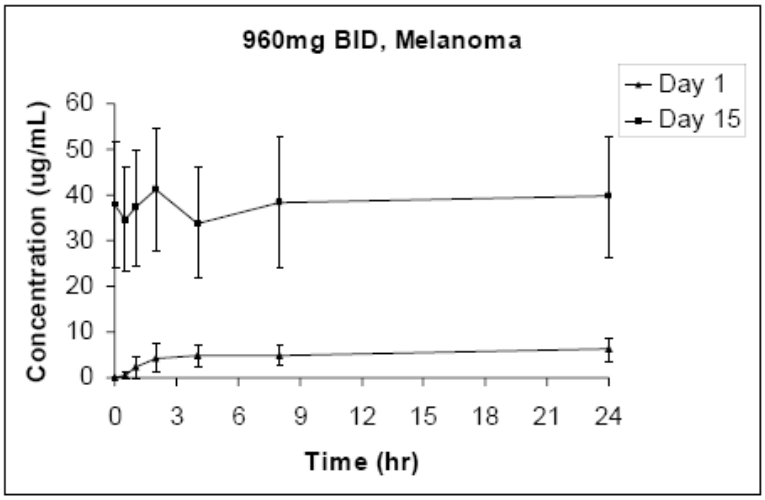


Note: The 3 patients who received 960 mg RO5185426 bid during the dose escalation phase are included in the melanoma extension cohort.

Pharmacokinetics evaluated in the melanoma extension phase revealed that VEM concentrations increased with time and became relatively flat after C_{max} was reached. On Day 15 VEM concentrations remained relatively flat throughout the twice daily dose interval as indicated in Figure 6. The median T_{max} for Day 1 and Day 15 were 4 h and 1 h respectively. AUC and C_{max} values increased from Day 1 to Day 15 as expected based on the VEM accumulation findings observed in patients during the dose escalation phase. The mean peak to trough ratio for VEM concentrations to Day 15 was 1.24 with a standard deviation (SD) of +/-0.2 and ranges from 1 to 1.63 in 12 patients, which indicated relatively consistent VEM plasma exposure during the dosing intervals. In this analysis the peak VEM concentrations reported for the morning dose and the trough concentrations of the evening dose in the twice daily dosing interval. Large inter-patient differences in VEM exposure were observed.

Figure 6.

PLX06-02: Mean RO5185426 Concentration versus Time Profile on Day 1 and Day 15 – Melanoma Extension (Linear Scale ± SD)



Relative bioavailability studies were conducted. For assessment of MBP capsules 80 mg versus 120 mg which was undertaken in the melanoma extension phase of study, differences in mean dose normalised exposure was no greater than 10%.

Assessment of the relative bioavailability of VEM in the 240 mg film coated tablets compared to the 120 mg capsules could not be assessed as data was only available for three patients.

Study PLX102-01

Study PLX102-01 was a randomised open label three-period crossover study with a primary objective of assessing the relative bioavailability of the two MBP formulations, that is, 40 mg capsule wet granulation and 40 mg capsule dry granulation compared to the reference crystalline formulation with capsule 300 mg, 900 mg doses used in the earlier PLX06-02 study. Eighteen healthy male subjects received the Phase I reference formulation and each of the MBP formulations, all administered as a single oral dose according to the assigned randomised sequence. During each treatment period VEM was administered following an overnight fast; subjects continued to fast for 4 h postdose at which time they were given a standardised meal. A washout period of 14-21 days separated each VEM dose.

All PK parameters were measured by individual listings and descriptive summary statistics by treatment. Primary study variables were assessed with the relative bioavailabilities of the new oral formulations $AUC_{0\text{-infinity}}$ or $AUC_{0\text{-last}}$ and C_{max}. To test the possible differences among formulations and analysis of variance (ANOVA) with factored formulation and period was applied to log transformed values of $AUC_{0\text{-infinity}}$ or $AUC_{0\text{-last}}$ and C_{max}.

The results of PLX102-01 demonstrated that each of the MBP 40 mg capsule formulations showed exposures ($AUC_{0\text{-infinity}}$) approximately 5 fold higher compared to the reference Phase I formulation. C_{max} levels were also greater for both MBP formulations versus the reference formulations. At the confidence interval (CI) interval of the $AUC_{0\text{-infinity}}$ exposure ratio, the two MBP formulations being 0.85 – 1.35 and outside the range of 0.8 to 1.25 the equivalence of the two MBP formulations could not be claimed.

Study NP22676

Study NP22676 was an open label multicentre Phase I study to evaluate the effect of VEM on the pharmacokinetics of five CYP450 substrates given as a drug cocktail. On Day 1, patients received single doses of the five probe drugs followed by a 5 day washout period. Blood samples were collected from Days 1-5 (treatment Period A) to establish a baseline PK profile for the five probe drugs and their major metabolites when administered without VEM. On Day 6 patients began receiving oral doses of VEM at 960 mg twice daily (treatment Period B). Blood samples were collected on Day 19 to establish the steady state PK profile for VEM monotherapy. On Day 20 the five probe drugs and VEM were co-administered. Blood samples were collected from Day 20 to Day 25 (treatment Period C) to establish PK profiles of the five probe drugs and their respective metabolites when co-administered with VEM. The cocktail of drugs involved included caffeine, warfarin, omeprazole, dextromethorphan and midazolam.

A total of 25 patients were enrolled on study and a statistical analysis of AUC, C_{max} and oral clearance (CL-F) for the CYP substrate parent and metabolite after administration with VEM was undertaken. After 15 continuous days of 960 mg twice daily VEM and single dose administration of five CYP450 substrates:

- CYP1A2 inhibition was observed when a single dose of caffeine was co-administered after a repeat dosing with VEM for 15 days. This resulted in a caffeine paraxanthine

AUC_{last} ratio of 0.45 between the two treatment periods with an average 2.5-fold increase and a maximum of up to 10-fold in caffeine plasma exposure after VEM treatment.

- VEM would be expected to increase plasma exposure of drugs predominantly metabolised by CYP1A2 which may result in a safety concern for CYP1A2 substrates with a narrow therapeutic index.
- CYP3A4 induction was observed when a single dose of midazolam was co-administered after repeat dosing with VEM for 15 days. This resulted in the midazolam/OH midazolam AUC_{last} ratio of >2 between the two treatment periods with an average of 32% decrease and a maximum of 80% in midazolam plasma exposure after VEM treatment.
- VEM would be expected to decrease plasma exposure of drugs predominantly metabolised by CYP3A4, which may result in a reduced therapeutic benefit from CYP3A4 substrates that have a steep exposure/response for efficacy although exhibit tolerance with chronic use such as certain opiates.
- No drug interaction was observed between VEM and omeprazole (CYP2C19 substrate). Small potential for interaction between VEM and peak exposure of omeprazole are not expected to have clinical implications.
- No drug interaction was observed between VEM and the metabolism of dextromethorphan (CYP2D6 substrate). An increase in the mean extent of exposure of both dextromethorphan and its metabolite upon co-administration with VEM without a concomitant change in the parent/metabolite ratio was observed. The reason for this observation is unknown.
- No drug interaction was observed between VEM and VEM/S-warfarin (CYP2C9 substrate) based on the statistical equivalence criteria in the study. However the increase in extent of S-warfarin exposure in its concomitant use with VEM with a mean AUC of 20% capital with the nonclinical signal for CYP2C9 inhibition and the inherent propensity for coagulation disorders in patients with malignant disease, warrant caution when VEM is co-administered with warfarin in patients with melanoma and when co-prescribing low therapeutic index medications primarily metabolised by CYP2C9.

Study NP25158

Study NP25148 was Phase I trial to characterise the mass balance, metabolism, routes and rates of elimination of carbon 14 labelled VEM. Patients received non-labelled VEM from Day 1 – 14 and received a single dose of carbon 14 labelled VEM on the morning of Day 15. Blood, urine and faecal sample collections for radioactivity accounting on the evening of Day 14 prior to administration of the radioactive dose and continued until the level of radioactivity recovered from urine, faeces was <1% of the radioactivity in the administered dose between the two successive 48-interval assessments.

A total of six patients who had metastatic BRAF V600 mutation test positive metastatic melanomas were fully evaluated. The results showed:

- The majority of the input radioactivity was recovered in faeces being 94% with a very small proportion being <1% recovered in urine.
- Limited extent of VEM metabolite formation in the systemic circulation was apparent in the profile of human plasma. The parent compound was the predominant component in all analysed plasma samples. Mean spectrometric data

indicated the potential metabolites in human plasma represented <5% of the total chromatographic radioactivity. Over the period investigated of 0-96 hours, potential metabolites each counted for <0.25% of the total administered dose in urine and <6% of the total administered dose in faeces. Therefore renal excretion played a minimal role in the disposition of VEM.

- Limited hepatic metabolism[19] and excretion of the parent molecule and its metabolites via bile into faeces is the likely predominant elimination route for VEM.
- Based upon the liquid chromatography coupled to mass spectrometry (LC/MS) profiles no new metabolites were detected in plasma and faeces in this study that were not observed in the nonclinical studies with rat and human hepatocytes and *in vitro* in rats and dogs. The chemical structure of human metabolites had not been determined.

Study NP25163

Study NP25163 was a randomised open label multicentre Phase I trial to characterise the PK profile of single and multiple dose VEM, using 240 mg twice daily MBP film coated tablets administered orally in previously treated patients with $BRAF^{V600}$ mutation positive metastatic melanoma with unresectable stage IIIC or stage IV disease. A total of 52 patients were enrolled onto study.

The study components consisted of screening, Period A, Period B, Period C and follow up. During Period A, Day 1 to the morning of Day 15, patients received dosing regimens according to their respective cohorts, 240 mg twice daily, 480 mg twice daily, 720 mg twice daily and 960 mg twice daily. Blood samples were collected on Day 1 to characterise single dose VEM exposure on Days 2, 9, 11 and 15 to characterise multiple dose exposure. During Period B, Day 16 to Day 21, the drug was held for the purpose of characterising the elimination profile of VEM. During Period C, starting on Day 22, all patients due to receive VEM at 960 mg twice daily until the development of progressive disease, unacceptable toxicity, consent withdrawal or any other criteria for removal.

The summary statistics of AUC, C_{max}, T_{max}, CL-F and $T_{1/2}$ for VEM on Day 1 and 15 are given in Tables 4 and 5 respectively.

The main findings of the study include:

- The mean dose normalised PK exposure (C_{max}) and the extent of exposure (AUC) of VEM in the study increased proportionally to the dose in the range of 240 mg to 960 mg twice daily despite the large overlap in the distribution of individual exposure values between doses.
- Approximately one third of the overall study populations and 41.6% of patients in the 960 mg twice daily dose cohort attained steady state in plasma by Day 15 on the individual based statistical analysis. The majority of remaining patients obtained 60-80% of the expected steady state exposure by Day 15 with the then concentration plasma exceeded the efficacy target from non-clinical studies.
- VEM exhibited marked accumulation after continuous twice daily dosing for 15 days with comparable mean extent and similarly high inter-patient variability for the 240-960 mg dose range.

[19] Sponsor comment: "By CYP3A4."

- No dose dependence of the mean terminal phase elimination half-life ($T_{1/2}$) or mean CL-F values was identified when characterised during the treatment interruption for seven days.
- The mean C_{trough} values in cycles 2-7 in Period C, that is, 960 mg twice daily range from 52-58.49 µg/ml consistent with trough values found in other studies.
- For the 960 mg twice daily dose the terminal elimination half-life determined after dose interruption for seven days was 34.1+/- 19.7 hours. For patients requiring dose interruption due to adverse events, VEM concentration would be reduced by half for each 34 h of dose interruption leading to the clearance of most of the drug from plasma within seven days.
- Repeat dosing with VEM 240, 480, 720 and 960 mg twice daily was associated with mean QTc prolongation[20] with the largest mean QTcF change from baseline observed in Period A post dose on Day 15 in all four cohorts with a range of 9.7 to 21 ms. The size of the mean QTc change from baseline did not exhibit a dose related trend during Period A.
- Mean QTc prolongation decreased during Period B when no drug was taken and increased during Period C when all patients were assigned to daily treatment with 960 mg twice daily of VEM. The mean QTc change from baseline in Cycle 2 and beyond was comparable to that observed in the corresponding phase of the VEM study.

[20] QT_c: The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated.

Table 4 NP25163: Summary Statistics of Pharmacokinetic Parameters for Each Dose Cohort on Day 1

Pharmacokinetic parameters for period A & B
Protocol(s): NP25163
Analysis: PK POPULATION

Visit=Day 1

Parameters	Statistics	Cohort1	Cohort2	Cohort3	Cohort4
AUC 0-8hrs(µg·h/mL)	n	12	12	12	16
	Arithmetic mean	8.3	13.8	21.9	27.0
	Median	6.3	15.0	20.2	22.9
	Standard deviation	6.13	7.72	12.97	18.87
	Coefficient of variation (%)	73.9	55.8	59.3	69.9
	Minimum ,Maximum	1.18,18.24	2.72,28.10	8.48,53.43	2.83,57.65
AUC 0-24hrs(µg·h/mL)	n	11	12	9	16
	Arithmetic mean	40.9	62.4	111.6	130.6
	Median	33.4	67.1	107.8	118.8
	Standard deviation	23.43	35.71	34.22	71.78
	Coefficient of variation (%)	57.3	57.2	30.7	55.0
	Minimum ,Maximum	11.50,88.24	16.48,138.58	75.43,184.07	20.21,247.19
Cmax 0-8hrs (µg/mL)	n	12	12	12	16
	Arithmetic mean	1.9	2.6	4.4	4.8
	Median	1.3	2.8	4.1	4.1
	Standard deviation	1.66	1.56	1.98	3.34
	Coefficient of variation (%)	85.3	60.5	44.6	69.8
	Minimum ,Maximum	0.26,5.82	0.56,5.88	1.96,9.46	0.61,10.70
Tmax 0-8hrs(hr)	n	12	12	12	16
	Median	4.0	4.0	5.0	5.0
	Minimum ,Maximum	1.92,8.00	1.95,5.00	2.00,8.08	2.00,8.00

Table 5 NP25163: Summary Statistics of Pharmacokinetic Parameters on Day 15 for Each Dose Cohort

Pharmacokinetic parameters for period A & B
Protocol(s): NP25163
Analysis: PK POPULATION

Visit=Day 15

Parameters	Statistics	Cohort1	Cohort2	Cohort3	Cohort4
AUC 0-8hrs(µg·h/mL)	n	10	9	9	11
	Arithmetic mean	117.8	233.8	343.3	392.2
	Median	94.2	254.7	424.2	426.2
	Standard deviation	50.52	106.93	151.23	126.37
	Coefficient of variation (%)	42.9	45.7	44.1	32.2
	Minimum ,Maximum	78.86,235.96	44.08,420.40	103.21,504.75	217.27,575.72
AUC 0-24hrs(µg·h/mL)	n	10	10	9	11
	Arithmetic mean	317.7	598.8	1003.7	1126.0
	Median	268.9	669.5	1171.5	1204.0
	Standard deviation	133.34	297.44	441.36	423.01
	Coefficient of variation (%)	42.0	49.7	44.0	37.6
	Minimum ,Maximum	195.97,617.56	89.36,1018.00	377.61,1546.38	629.75,2068.52
AUC 0-168hrs(µg·h/mL)	n	10	8	9	11
	Arithmetic mean	920.3	2243.5	3127.1	3530.3
	Median	747.6	2453.4	3253.7	3322.5
	Standard deviation	538.35	1336.15	1789.97	1811.43
	Coefficient of variation (%)	58.5	59.6	57.2	51.3
	Minimum ,Maximum	498.87,1917.53	110.90,4281.70	758.12,6119.55	1334.3,7477.13
Cmax 0-168hrs (µg/mL)	n	10	9	9	11
	Arithmetic mean	17.2	35.4	52.7	61.4
	Median	13.4	38.9	59.1	59.7
	Standard deviation	7.43	17.44	22.40	22.76
	Coefficient of variation (%)	43.1	49.2	42.5	37.1
	Minimum ,Maximum	10.90,32.20	6.86,67.50	18.50,77.80	31.20,106.00

Table 5. Continued

Visit=Day 15

Parameters	Statistics	Cohort1	Cohort2	Cohort3	Cohort4
Tmax 0-168hrs(hr)	n	10	9	9	11
	Median	4.0	2.3	2.0	2.0
	Minimum ,Maximum	0.00,8.00	0.00,5.00	0.00,24.17	0.00,24.00
CL/F (L/hr)	n	10	8	9	11
	Arithmetic mean	0.3	0.8	0.4	0.3
	Median	0.3	0.2	0.2	0.3
	Standard deviation	0.13	1.45	0.28	0.19
	Coefficient of variation (%)	39.3	189.3	81.0	53.5
	Minimum ,Maximum	0.13,0.48	0.11,4.33	0.12,0.95	0.13,0.72
t1/2 (hr)	n	10	10	9	11
	Arithmetic mean	31.5	38.4	34.9	34.1
	Median	25.9	36.7	28.6	25.4
	Standard deviation	19.05	24.18	19.48	19.66
	Coefficient of variation (%)	60.4	63.0	55.9	57.7
	Minimum ,Maximum	15.88,80.92	8.19,89.09	14.06,72.98	13.92,65.72

*The values of PK parameters calculated for 0-168 hours on Day 15 represent values from Day 15 to predose on Day 22.

Study NP22657: QT interval sub-study

Study NP22657 was a principal supportive efficacy study, being an open label multicentre single agent uncontrolled Phase II study in previously treated patients with $BRAF^{V600}$ mutation positive Stage IV melanoma and included a sub-study to investigate the effects of VEM on the QT interval and to correlate VEM exposure with the ECG parameters.

Five serial ECGs, that is, time matched baseline ECGs were taken during screening on Days 1 and 15 on Cycle 1 on Day 1 of Cycles 2, 4, 6 and 10 on Day 1 of every other three week cycle, that is, every six weeks. To determine the effect of VEM on the ECG including the QT interval, that is, the maximum time match change from baseline to the QTc interval and each post baseline timepoint, blood samples for concentration of VEM were obtained immediately after each set of serial ECGs was taken.

VEM did not appear to have a clinically meaningful effect on heart rate. The regression model of QT analysis was used to determine the best correlation for heart rate. In this study, QTcP eliminated most of the bias from the QT-RR relationship; therefore QTcP was used for the primary statistical analysis of QTc interval variables.

Repeat dosing with VEM 960 mg twice daily was associated with mean prolongation of the QTc interval of 12-15ms from Cycle 2 and after with the largest being QTcP prolongation observed in Cycle 6, being 15.1 ms with an upper 95% CI of 17.7 ms. There was a low incidence of QTcP >500ms in two patients and QTcP change from baseline >60 ms in one patient. There were no reported AEs in these patients that could be potentially associated with either QT prolongation or arrhythmia. VEM did not appear to affect the heart rate, PR or QRs intervals or new T wave morphology. A 14.8% incidence of new abnormal T wave morphology was detected.

The extent of QTc prolongation exhibited a positive relationship with VEM concentration in plasma. A population approach was utilised to fully characterise the exposure/effect relationship. The PK findings from the overall PK analysis population in NP22657 study include:

- Based on the accumulation ratio derived from $AUC_{0\text{-}8\ h}$ on Day 1 and 15, VEM exhibited 14 to 17 fold accumulation at the expected study state in plasma after dosing of 960 mg twice daily for 15 days with high inter-patient variability in the rate of accumulation and extent of exposure in plasma.
- On average in 960 mg twice daily dose resulted in relatively consistent mean VEM exposures during the 24 h dosing period at the expected study state.
- Mean VEM exposure ($AUC_{0\text{-}8\ hours}$) was 42% higher in females among 27 patients than in males among 60 patients.
- VEM daily exposure at expected steady state ($AUC_{0\text{-}8\ hours}$) was attained with 960 mg twice daily in metastatic melanoma patients with the level predicted to elicit tumour response based on nonclinical studies.

Comparison and analyses of results across studies

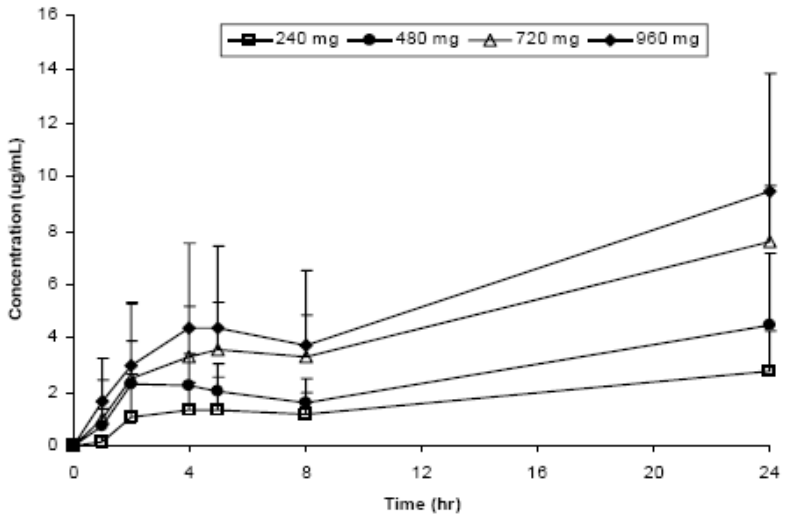
As previously indicated the clinical pharmacokinetics of VEM in this submission were obtained from PK data from the five Phase I studies, one Phase II study and one Phase III study. A summary of demographics across all these studies showed that the patient populations were generally comparable among studies where PK was evaluated.

Review of concentration time profiles accumulation and inter-patient variability was obtained from the Study NP25163. On Day 1 of this study mean plasma VEM

concentrations increased rapidly within the first two h reaching C_{max} at approximately 4 h following the first oral administration of VEM in each dosing cohort, as indicated in Figure 7. Median T_{max} values were 4-5 h across the four dose cohorts as indicated in Table 5. VEM concentrations for each dose cohort continued to increase following the second VEM dose at approximately 12 h as measured at the 24 h assessment timepoint. Steady state was approached on Day 15 VEM concentration time profiles across the four dose cohorts were relatively flat with peak to trough ratios ranging from 1.1 to 1.3 on Day 15 during the 24 h dosing period. The peak concentration in this ratio was measured after a morning dose on Day 15 (pre-dose) concentration on Day 15 resulting from the evening dose on Day 14.

Figure 7.

NP25163: Mean (± SD) RO5185426 Concentration vs Time Profile on Day 1 (AUC_{0-8h}, Linear Scale; 240 to 960 mg bid)



VEM exhibited marked accumulation after continuous dosing was observed with a mean value that was similar across the four dose cohorts, range 18.8 – 24.9 as indicated Table 6. Marked inter-patient variability in the rate of accumulation was comparable between dose cohorts. The accumulation ratio was defined as a ratio of AUC_{0-8h} on Day 15/$AUC_{0-8\ h}$ on Day 1.

Table 6.

NP25163: Mean RO5185426 Accumulation Ratios (AUC_{0-8h}) Day 15/Day 1 (240 to 960 mg bid)

	240 mg	480 mg	720 mg	960 mg
N	10	9	9	11
Mean	24.9	23.3	18.8	23.2
SD	29.4	16.0	12.4	16.5
Median	12.9	14.3	18.6	14.5
Min–Max	5.15–5.15–101.4	10.3 – 50.8	5.96 – 46.9	7.66 – 54.5

NOTE: Accumulation ratio is the ratio of AUC_{0-8h} on Day 15/AUC_{0-8h} on Day 1.

High inter-patient variability in extent of VEM exposure was observed among the four dose cohorts evaluated in Study NP25163 leading to overlap among dose levels. On average the C_{max} and $AUC_{0-8\ h}$ CV percentage were approximately 65% after the first dose on Day 1 across the dose range tested. Following multiple doses on Day 15 the CV percentage of C_{max} and $AUC_{0-8\ h}$ across the dose range were approximately 43 and 41%

respectively as indicated in Table 5. Inter-patient variability is unlikely to be dose related and there is no clear trend in CV percentage observed across dose cohorts. Inter-patient variability in the individual VEM concentrations on Day 15 for each dose cohort following oral administration of 240-960 mg twice daily is given in Figures 8 and 9.

Figure 8.

NP25163: Individual RO5185426 AUC_{0-8h} Values on Day 15 for Each Dose Cohort (240 to 960 mg bid)

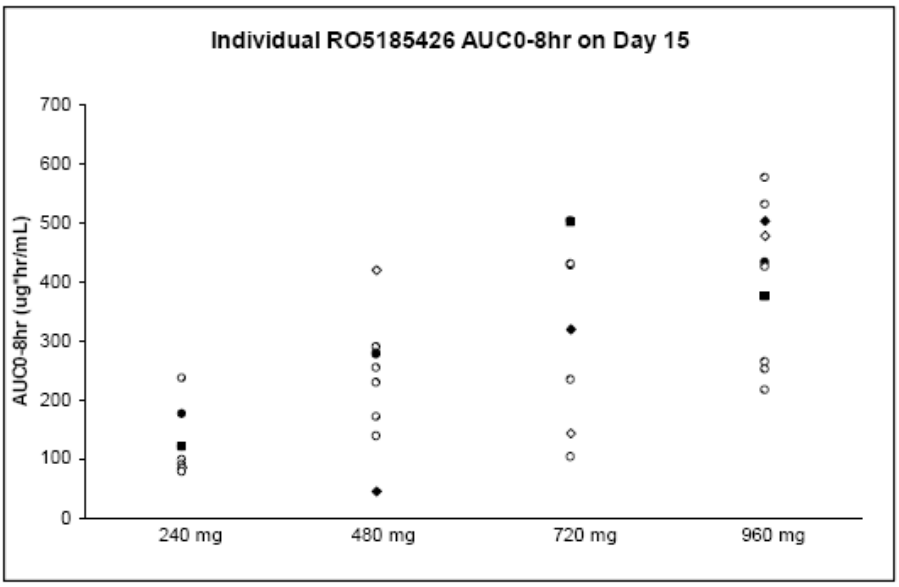
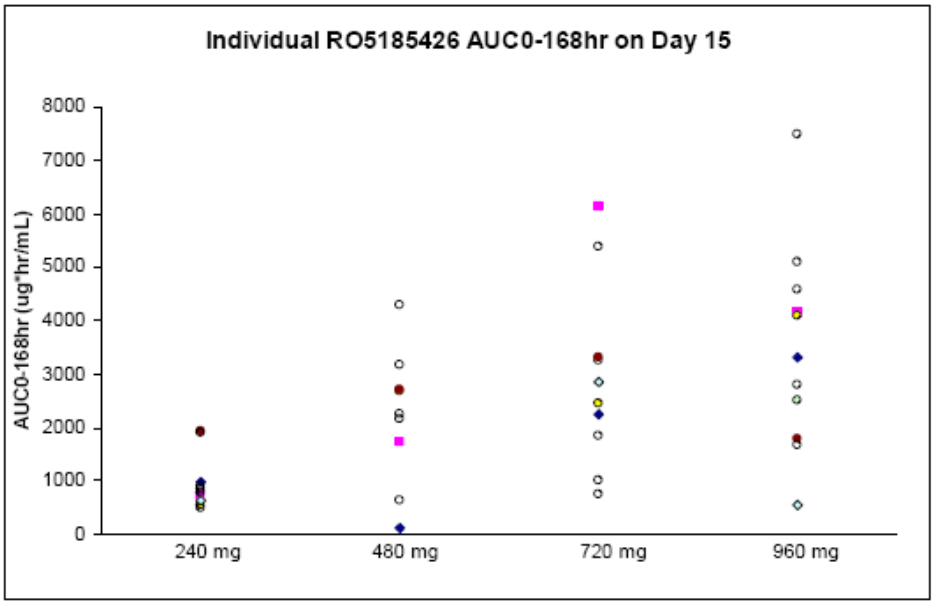


Figure 9.

NP25163: Individual RO5185426 AUC_{0-168h} Values on Day 15 for Each Dose Cohort (240 to 960 mg bid)



Reviewing dose proportionality: In Study PLX06-02 the rate and extent of VEM exposure and plasma increase of doses in patients received 160-1120 mg twice daily with the MBP capsule formulation. Classic representation of dose normalised mean values suggested that both C_{max} and $AUC_{0-8\ h}$ appeared to be proportional with doses between 240 mg and 960 mg, although with high inter-patient variability.

Study NP25163 assessed the dose proportionality of VEM using the 240 mg MBP film coated tablet formulation the same dose range observed in PLX06-02. The dose normalised VEM exposures are provided Table 7 and Figures 10, 11, 12 and 13. Statistical analysis of key pharmacokinetic parameters supported dose proportionality of the VEM exposure from 240-960 mg twice daily administered as the MBP film coated tablets. Results of the one-way ANOVA test for VEM dose proportionality and the corresponding P values indicated that the null hypothesis of equal treatment effects for the relevant VEM treatment exposure parameters, AUC and C_{max} among the four dose cohorts cannot be rejected for PK parameters tested.

Table 7.

NP25163: Summary of Dose Normalized RO518546 Exposure across all Cohorts (240 to 960 mg bid)

	240 mg	480 mg	720 mg	960 mg
AUC_{0-8h} µg·h/mL				
N	10	9	9	11
Mean	0.491	0.487	0.477	0.409
SD	0.21	0.223	0.21	0.132
CV%	42.9	45.7	44.1	32.2
AUC_{0-24h} µg·h/mL				
N	10	10	9	11
Mean	1.324	1.247	1.394	1.173
SD	0.556	0.62	0.613	0.441
CV%	42	49.7	44	37.6
AUC_{0-168h} µg·h/mL				
N	10	8	9	11
Mean	3.835	4.674	4.343	3.677
SD	2.243	2.784	2.486	1.887
CV%	58.5	59.6	57.2	51.3
C_{max} µg/mL				
N	10	9	9	11
Mean	0.072	0.074	0.073	0.064
SD	0.031	0.036	0.031	0.024
CV%	43.1	49.2	42.5	37.1

NOTE: Patients were dosed with 4-different bid doses for 14 days. On Day 15, each patient received a morning dose and then RO5185426 was withheld until Day 22; AUC_{0-8h}, AUC_{0-24h} and AUC_{0-168h} were calculated following the morning dose on Day 15; C_{max} was determined over the 168 hour interval following the Day 15 morning dose.

Figure 10.

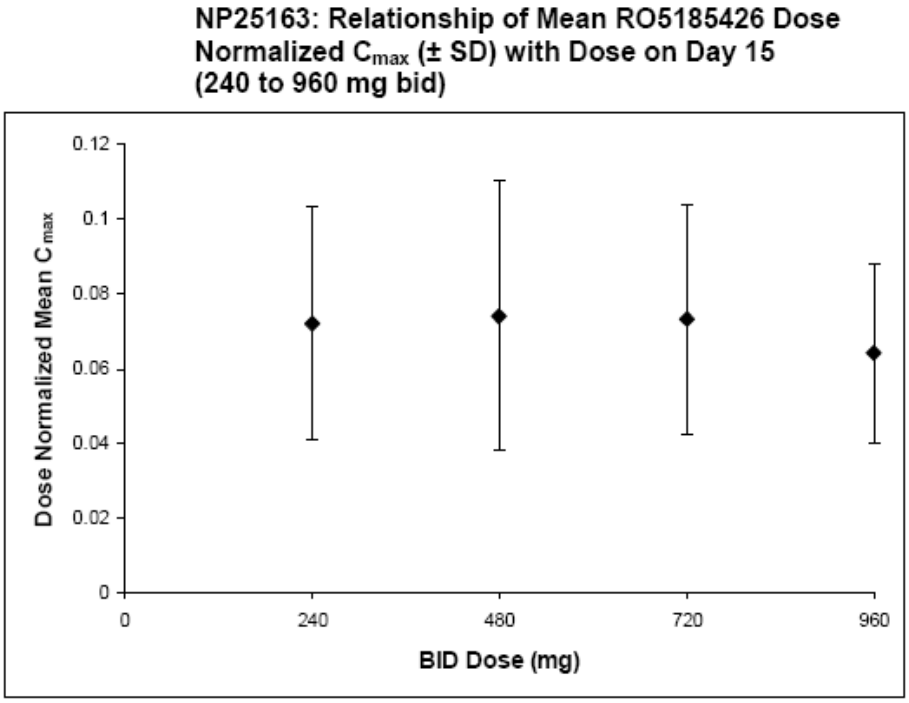


Figure 11.

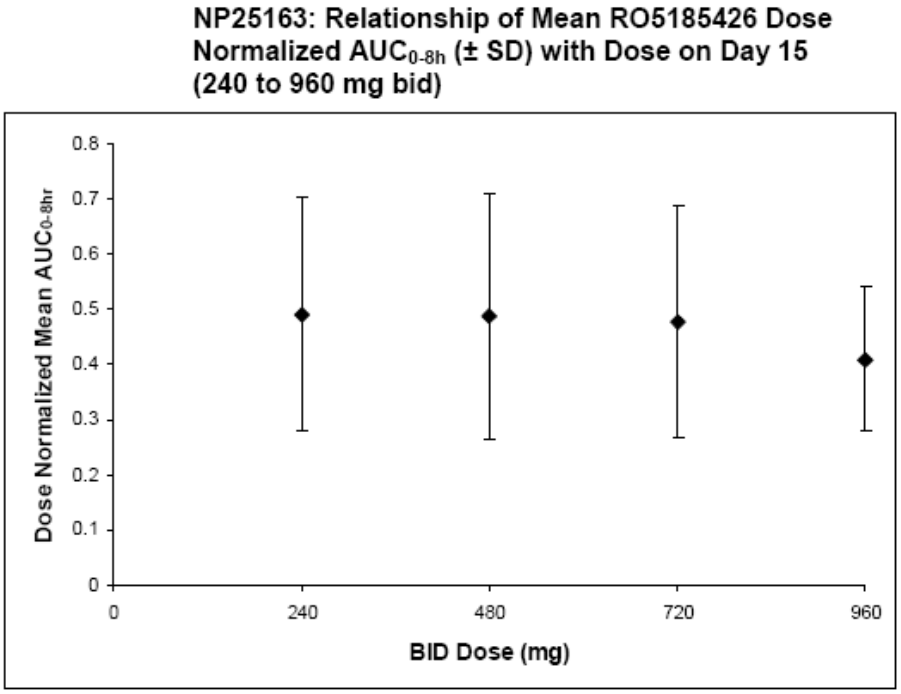


Figure 12.

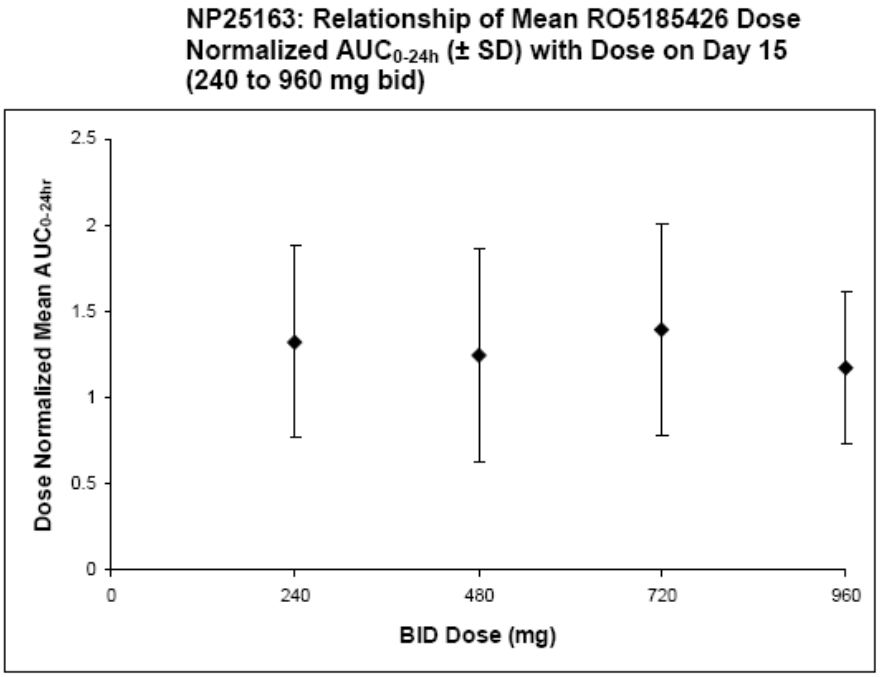
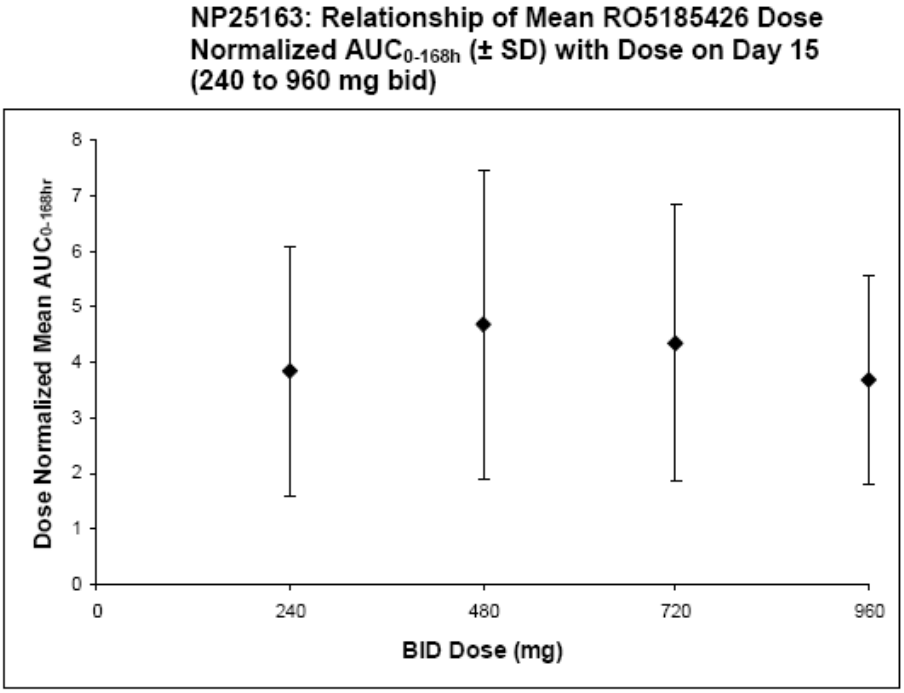


Figure 13.



Elimination half-life: The only study which can provide data in relation to this was NP25163 and no dose dependence on the mean terminal phase of elimination half-life ($T_{1/2}$) or mean CL-F values were identified when this parameter was characterised after treatment interruption of seven days. The mean elimination half-life values across the four dose cohorts were 31.5, 38.4, 34.9 and 34.1 h for 240, 480, 720 and 960 mg twice daily doses respectively. These results with the 960 mg twice daily cohort would be indicative of the elimination profile of VEM in patients whose treatment was interrupted. Analysis of

mean trough data following VEM dose interruption indicates that 95% of VEM is cleared from plasma.

Approach to steady state: Both individual based and aggregate approaches were utilised in Study NP25163 to assess the post dose steady state and suggested that earlier possibly 35% of patients on the individual base methods in the overall study population and 41.6% of patients in the 960 mg dose cohort had reached steady state by Day 15. This is indicated in Table 8. The key steady state characteristics were qualitative similar across the four dose cohorts. With the aggregate method steady state was not achieved up to Day 9. There was a similar pattern across the four dose cohorts in that the mean percentage of the projected steady state exposure that was attained was about 15-20% on Day 2 and 60-80% on Days 9, 11 and 15.

Table 8.

NP25163: Summary Statistics of the Time to Steady State for All Dose Cohorts (240 to 960 mg bid)

	Total	240 mg	480 mg	720 mg	960 mg
Total number (n)	52	12	12	12	16
Evaluable for SS (n)	43	11	11	9	12
Achieved SS (n)	15	3	2	5	5
Mean (days)*	12.08	14.69	8.6	10.37	13.6
Median (days)*	14.11	14.93	8.6	11.27	14.81
Standard deviation*	3.94	0.5	2.53	5.25	2.73
Min (days)*	3.59	14.11	6.82	3.59	9.09
Max (days)*	15.99	15.02	10.39	15.63	15.99

Evaluation for SS: Number of patients with at least 3 C_{trough} on Days 2, 9, 11, 15.
Achieved SS: Number of patients who reached steady state.
*Computed based on population who achieved SS.

Apparent volume of distribution: Data from Study NP22676 revealed that the mean $AUC_{0\text{-}tau}$ for 20 patients was approximately 600 pg.hour/ml, whereby the tau was 12 hours. In Study NP25163 the elimination rate constant at a 960 mg dose after a seven day drug interruption was 0.020/hours with a similar estimate for $AUC_{0\text{-}tau}$. From these data, VDF-F can be estimated from steady state values to be approximately 80 litres.

Cross study comparison of single and multiple doses VEM at 960 mg twice daily.

The VEM concentration time profiles and calculated parameters are for the first dose were compared to data collected after multiple twice daily doses generally at Day 15. Data as shown in Figure 14 for Study NP22657, are generally representative of VEM exposure observed in other studies with the 960 mg twice daily dose. After the first dose VEM concentration rises rapidly within the first 2 h and reaches C_{max} generally within 4 h at which point plasma concentrations are relatively flat. VEM concentrations continue to rise with repeat twice daily dosing until steady state is reached within 22 days for most patients. Once steady state is approached the concentration time profile across the dose intervals is characteristically flat in all studies evaluated. For 85 patients in the primary PK population in Study NP22657, the mean peak to trough ratio for VEM concentrations on Day 15 was low, being 1.13 indicating relatively consistent VEM exposure in plasma during the dosing interval. Similar results were found for 960 mg dose cohort in the NP25163 study. Comparison of the VEM pharmacokinetic parameters from Studies NP22657 and NP25163 showed the typical increase in exposure observed following 15 days of 960 mg twice daily dosing as indicated in Table 9. The ratio between the mean values on Day 15 and Day 1 from both studies range from 15 to 17 fold for $AUC_{0\text{-}8\ h}$ and 13 to 14 fold for AUC for C_{max}. The individual Day 15/Day 1 ratios for patients in both studies for the 960 mg dose showed a wide variability among patients ranging from approximately 6>100-fold as indicated in Table 10. In Study NP22657, an analysis of VEM

concentrations 4 h post dose on Day 1 and Day 15 in 102 patients assessed on both days, showed a wide distribution of value and accumulation. Mean dose values on Day 1 and Day 15 were 3.6+/-2 µg/ml and 49.0+/-22.5 µg/ml respectively.

Figure 14 **NP22657: Mean RO5185426 Concentration versus Time Profile on Day 1 and Day 15 (Log Scale ± SD; 960 mg bid)**

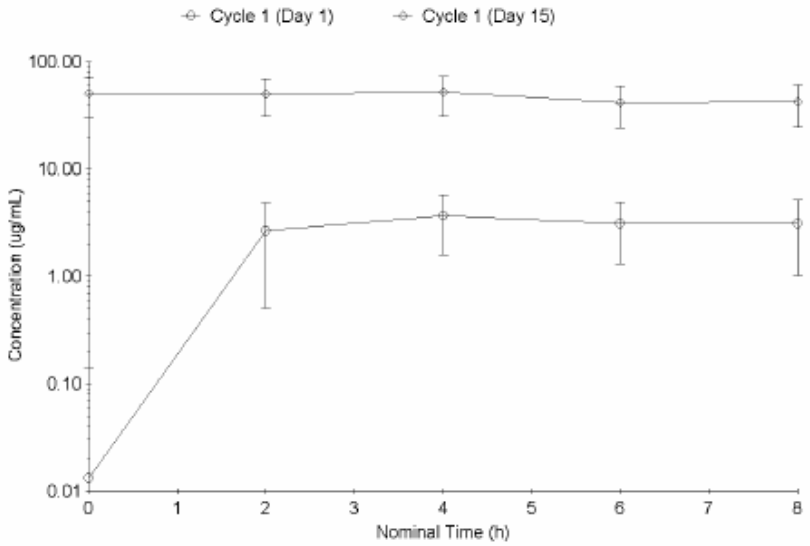


Table 9.

NP22657 and NP25163: Comparison of Pharmacokinetic Parameters on Day 1 and Day 15 (960 mg bid)

Parameters	NP22657		NP25163	
	Day 1	Day 15	Day 1	Day 15
$AUC_{0\text{-}8h}$ [a] (µg·h/mL)	22.1 ± 12.7 (57.6) (3.5–56.4, n=88)	380.2 ± 143.6 (37.8) (66.2–903.9, n=87)	27.0 ± 18.9 (69.9) (2.8–57.7, n=16)	392.2 ± 126.4 (32.2) (217.3–575.7, n=11)
C_{max} [a] (µg/mL)	4.1 ± 2.3 (56.6) (0.64–11.8, n=88)	56.7 ± 21.8 (10.2–118.0, n=87)	4.8 ± 3.3 (69.8) 0.61–10.7, n=16)	61.4 ± 22.8 (37.1) [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 (CV%), (Min–Max values, Number of patients evaluated).
[b] Median (Min-Max), Number of patients.
[c] Time interval of assessment equals 0-168 hours.

Table 10.

NP22657 and NP25163: Mean RO5185426 Accumulation Ratios[a] for RO5185426 (960 mg bid)

	NP22657	NP25163
N	83	11
Mean	24.1	23.2
SD	20.9	16.5
CV%	86.7	71.1
Median	17.2	14.5
Min–Max	5.64–116.7	7.66–54.5

[a] Accumulation ratio is the ratio of $AUC_{0\text{-}8h}$ on Day 15/ $AUC_{0\text{-}8h}$ on Day 1.

VEM pharmacokinetic parameters on Day 15: A comparison of mean PK parameters after 15 days of VEM dosing at 960 mg twice daily from three clinical trials using 240 mg MBP film coated tablets, that is, Studies NP22657, NP22676 and NP25163 and one study using the 120 mg MBP capsules (Study PLX06-02 melanoma extension) is indicated Table 11. The mean $AUC_{0\text{-}8\ h}$ and C_{max} values for the three studies using the 240 mg film coated tablets are within 10% of each other showing relative agreement.

Table 11.

Comparison of RO5185426 Pharmacokinetic Parameters on Day 15 in Studies NP22657, NP25163, N22676 and PLX06-02 (960 mg bid)

Parameters	NP22657 n=87	NP25163 n=11	NP22676 n=21	PLX06-02 [e] n=14
$AUC_{0\text{-}8h}$ [a] (µg·h/mL)	380.2 ± 143.6 (37.8) (66.2 – 903.9)	392.2 ± 126.4 (32.2) (217.3–575.7)	422 ± 121 (28.7) (123–635)	289.3 ± 105.9 (36.6) (89.3–457.7)
C_{max} [a] (µg/mL)	56.7 ± 21.8 (10.2–118.0)	61.4 ± 22.8 (37.1) [c] (31.2–106.0)	61.7 ± 17.2 (27.9) 16.8–90.5)	44.3 ± 16.4 (37.0) (11.9–71.9)
T_{max} [b] (h)	2 (0–8.9) n = 88	2 (0–24) [c] n = 11	3 (0–26) [d] n = 21	1 (0–8) n = 14

[a] Mean ± SD (CV%), (Min–Max values, Number of patients evaluated)
[b] Median (Min-Max), n=Number of patients
[c] Time interval of assessment equals 0-168 hours
[d] Time interval of assessment equals 0-26 hours
[e] Melanoma Extension Cohort with 120 mg MBP capsules.

When comparing VEM exposure between the Study PLX06-02 and Study NP22657, the $AUC_{0\text{-}8\ h}$ and C_{max} values were 24% and 22% lower respectively using the 120 mg MBP capsules compared with the 240 mg MBP film coated tablets. These differences increased to 31% and 28% for $AUC_{0\text{-}8h}$ and C_{max} when comparing data from PLX067-02 and NP22676. Despite differences in sample sizes it appears that the 240 mg film coated tablets provided higher exposures on Day 15 at the 960 mg twice daily dose and the 120 mg MBP capsules.

Steady state and VEM trough values over time: The approach for steady state was formally evaluated in NP25163. Based on the individual based statistical approach, 5/12 patients in the 960 mg dose cohort achieved steady state and the remaining patients reached 60-80% of the projected steady state exposure up to 14 days of dosing at 960 mg and a morning dose on Day 15.

In a larger patient sampling in Study NP22657 involving 72 patients, analysis of VEM trough concentrations, that is, before the morning dose on Day 15 and 22 in patients without dose modifications up to and including Day 22, showed that 16 patients or 22.2% exhibited a 20% or greater increase in trough value on Day 22 compared with Day 15. It may therefore be extrapolated that approximately 80% of patients in NP22657 may have reached steady state by Day 15. The mean VEM trough values on Days 15 and 22 in this subset of patients were 48.9 µg/ml and 48 µg/ml respectively; the mean Day 22 to Day 15 ratio was 1.03 as indicated in Table 12.

Table 12.

NP22657: RO5185426 Trough Values and Trough Ratio on Day 15 and Day 22 (960 mg bid)

Summary Values [a]	Day 15	Day 22	Trough Ratio [b]
N	72	72	72
Mean ± SD (CV%)	48.85 ± 19.76 (40.45)	47.98 ± 18.69 (38.96)	1.03 ± 0.28 (27.46)
Median (min – max)	49.05 (6.97 – 118.0)	46.85 (10.7 – 111.0_	1.00 (0.58 – 2.07)

[a] Mean and median trough (predose) values are expressed as µg/mL.
[b] Ratio of trough (predose) values on Day 22/Day 15

Based on these observations it would be expected that a proportion of patients would not attain steady state of VEM in plasma by Day 15. The reasons for this inter-patient variability in process state are currently unknown. It should be noted that the VEM concentration on Day 15 in the vast majority of patients exceeded the nonclinical efficacious target of >400 µg/ml.

After Day 15, a relatively constant mean trough concentration, with range 41.1 to 58.3 µg/ml across the three Studies NP25163, NP22657 and N025026, was maintained throughout subsequent treatment cycles with relatively high inter-patient variability as indicated in Figure 15 and Table 13.

Figure 15.

RO5185426 Trough Values after Day 15 in Studies NP25163, NP22657, and NP25026 (960 mg bid)

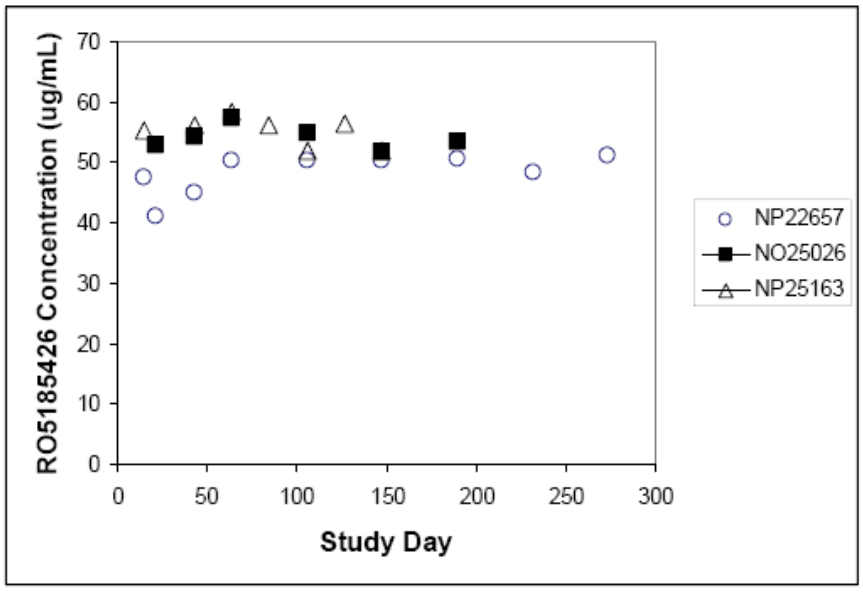


Table 13.

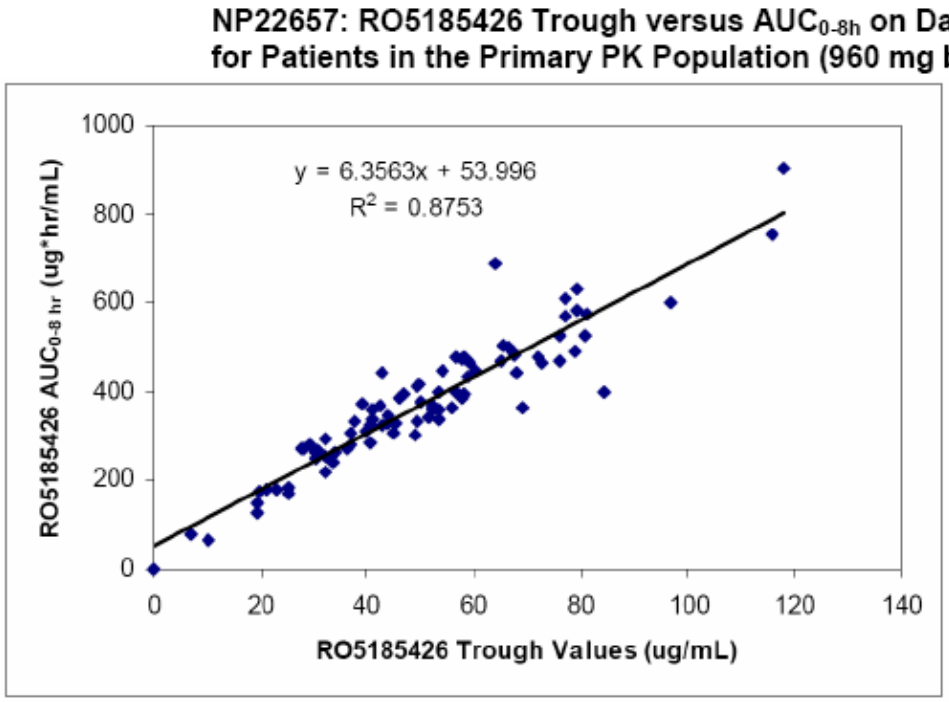
Comparison of Mean RO5185426 Trough Concentrations at and After Day 15 in Studies NP25163, NP22657, and NO25026 (960 mg bid)

Study Day	NP25163	NP22657	NO25026
15		47.55 ± 23.14 (48.7) (21-118, n=108)	NA
22	NA	41.12 ± 23.39 (56.9) (0-111, n = 122)	53.0 ± 26.66 (50.3) (0 – 121, n=204)
43	55.03 ± 27.53 (50.02) (10.5 - 97.6, n=37)	45.20 ± 21.33 (47.2) (0-96.6, n = 109)	54.4 ± 24.13 (44.4) (0 – 116, n=166)
64	59.40 ± 22.62 (26.26) (29.6 – 102, n=27)	50.31 ± 19.52 (38.8) (0-109, n=109)	57.4 ± 23.79 (41.5) (0.12 – 130, n=141)
85	56.2 ± 24.6 (43.8) (2.2-112, n=15)	NA	NA
106	52.09 ± 20.45 (39.25) (27.3 - 94.4, n=12)	50.38 ± 19.54 (38.8) (0.2-106, n=96)	55.0 ± 17.62 (32.0) (21.9 – 101, n=77)
127	56.5 ± 23.0 (40.7) (24.5-98.0, n=9)	NA	NA
148	51.97 ± 18.51 (35.62) (36.1 - 72.3, n=3)	50.42 ± 22.06 (43.8) (13.9-08, n=71)	51.8 ± 24.13 (46.6) (0 – 126, n=38)
190	NA	50.78 ± 20.19 (39.8) (0-95.2, n=50)	53.6 ± 12.6 (23.5) (31.8 – 73, n=9)
232	NA	48.48 ± 14.98 (30.9) (10.1-80.6, n=23)	NA
274	NA	51.27 ± 16.69 (32.5) (20-79.3, n=11)	NA

Mean ± SD (CV%), (Min–Max values, Number of patients evaluated; NA = Not Analyzed

In Study NP22657 a strong correlation between VEM $AUC_{0\text{-}8\ h}$ and trough concentration on Day 15 was observed in 72 patients in the primary PK population for whom both parameters were available as indicated in Figure 16. VEM consistently exhibited a relatively flat concentration time profile during the twice daily dosing intervals. The mean trough VEM concentrations were comparable for PK assessments after Day 15 thus, it could be expected that a similarly strong relationship would exist between VEM C_{min} and $AUC_{0\text{-}8\ h}$ across repeated treatment cycles.

Figure 16.



VEM inter-patient variability: VEM exhibited high inter-patient variability of the individual values of AUC and C_{max} across the four doses, 240-960 mg evaluated in NP25163. This finding was consistent across other studies in patients who received 960 mg for the parameters of AUC, C_{max}, accumulation, trough and post dose as indicated in Table 14.

Table 14.

Comparison RO5185426 AUC_{0-8h} and C_{max} CV% and Min–Max on Day 1 and Day 15 (960 mg bid)

Parameters	Study Day	NP25163	NP22657	NP22676
AUC_{0-8h} (µg·h/mL)	1	69.9% 2.8–57.7 (n=16)	57.6% 3.5–56.4 (n=88)	NA
	15	32.2% 217.3–575.7 (n=11)	37.8% 66.2– 903.9 (n=87)	28.7% 123–635 (n=21)
C_{max} (µg/mL)	1	69.8% 0.61–10.7 (n=16)	56.6% 0.64–11.8 (n=88)	NA
	15	37.1% 31.2–106.0 (n=11)	38.4% 10.2–118.0 (n=87)	27.9% 16.8–90.5 (n=21)

Across Studies NP25163, NP22657 and NP622676, the inter-patient variability for both AUC and C_{max} were generally higher after the first dose on Day 1 with a range of 57.6% to 69.9% than after multiple doses on Day 15 (range 27.9% - 38.4%). The reasons for these differences are not known.

Excretion: The mass balance Study NP25158 provided a reliable assessment of the rates and routes of VEM metabolism and excretion. The majority of parent molecule and metabolites were shown to be eliminated in the faeces for an average of 94% of the input radioactivity. The majority of this was associated with the parent molecule. Approximately half of the input radioactive dose was excreted as parent drug within the first 96 h. Renal

elimination account for <1% of the input radioactive dose with a mixture of lower levels of parent molecule and the two previously characterised metabolites.

These clinical results are consistent with the nonclinical PK studies in rats, which showed that the drug derived radioactivity parent but all metabolites was primarily recovered in faeces and the majority of the radioactivity led to unchanged parent drug. Furthermore the mass spectrometry indicated that the metabolites detected in this clinical study are the same as those previously identified *in vitro* in rats and human hepatocytes and *in vivo* studies in rats and dogs.

Absolute bioavailability: It was not possible to develop studies to assess absolute bioavailability as VEM is a drug with low solubility and permeability making it not possible to formulate standard doses of IV formulation.

Population pharmacokinetics analyses

Plasma concentrations of VEM collected in the Phase I, PK study NP25163, Phase II NP22657 and Phase III N025026 studies were pooled for the population PK analyses. The pooled data set consist of 5411 plasma concentrations for 458 patients with $BRAF^{V600}$ mutation positive metastatic melanoma. A summary of the number of plasma concentrations in patients included for each study is provided in Table 15.

Table 15.

Number of RO5185426 Plasma Concentrations and Patients Included in the Population PK Analyses by Study (NP25163, NP22657, NO25026)

Phase – Study Number	No. Plasma Concentrations	No. Patients
Phase 1 – NP25163	1382	52
Phase 2 – NP22657	2391	132
Phase 3 – NO25026	1638	274

Models with one and two open-compartments were tested with or without lag time with first order absorption or with sequential zero order and first order absorption. The compartmental models were parameterized in terms of clearance and volume of distribution. Data analyses were performed using non-linear mixed effect modelling as implemented in the software NONMEN version 7.1.0. Co-variates were selected based on their clinical relevance and potential effects on the PK parameters. The influence of the following baseline co-variates on the PK parameters was investigated:

- Demographic co-variates including age, BMI, body weight, ethnicity, gender, height and race.
- Laboratory co-variates including ALT, ALP, AST, bilirubin and creatinine clearance.
- Liver metastases status as presence or absence.

Results: The basic structural PK model is a one-compartment open model with first order absorption and first order elimination. The PK model parameters estimated are CL-F, V-F, absorption constant (KA) and relative bioavailability (F1). Between-patient variability is incorporated for parameters CL-F, V-F and KA in the basic PK models.

Only the co-variate gender was found to statistically influence the CL-F and the apparent volume of distribution with a 17% greater clearance and a 48% greater volume of distribution for male patients. All parameter estimates for the final PK model are indicated in Table 16. In addition the graphic comparisons of the individual estimated CL-F and V-F by gender are provided in Figure 17.

Table 16.

Parameter Estimates for the Final Population PK Model (NP25163, NP22657, and NO25026)

Parameter	Unit	Estimate	RSE (%)
Fixed Effects			
CL/F	L/day	29.3	2.70
V/F	L	90.9	6.67
KA	1/day	4.50	9.00
$F1_{\text{Cycle 1, Day 1 - Cycle 1, Day 14}}$ [a]	–	0.788	2.79
$F1_{\text{Cycle 1, Day 15 – C4}}$ [a]	–	0.899	1.84
F1 [b]	–	1 (fixed)	–
Random Effects BPV			
CL/F	CV%	31.9	8.78
V/F	CV%	64.8	14.1
KA	CV%	101	13.4
Correlation CL-V	–	0.43	-
Covariate Effects			
Effect of sex on CL/F	–	0.171	22.7
Effect of sex on V/F	–	0.479	24.0
Error Model			
σ_1 (additive)	µg/mL	0.818	9.03
σ_2 (proportional)	%	22.8	2.71
RUNID: RUN083, OFV: 27069.372			

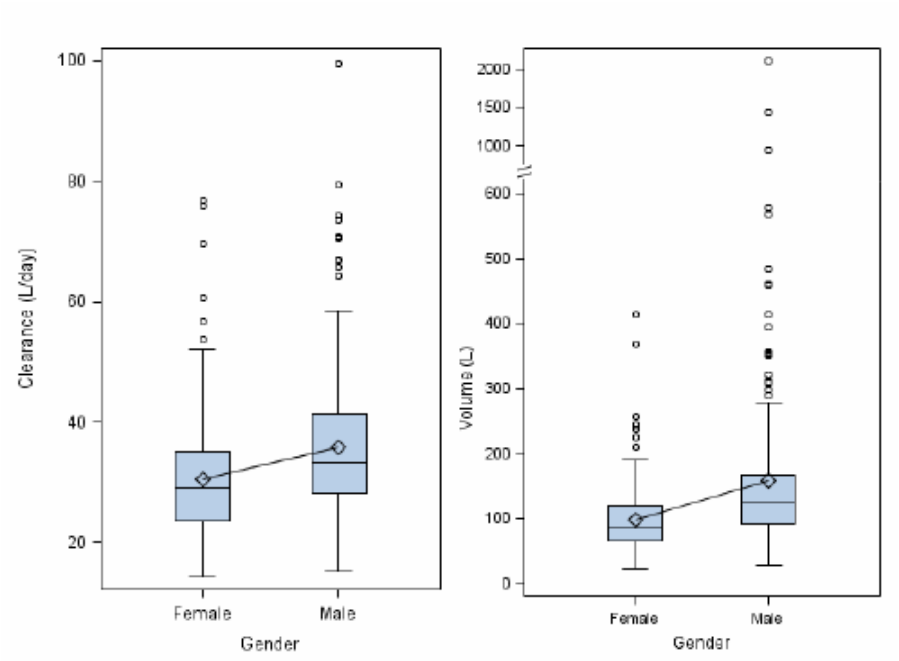
BPV = between-patient variability; σ = Standard error; **RSE** = Relative standard error of estimate; **OFV** = Objective function value; **Sex** = Gender.

[a] F1 for Phase 1PK/PD (NP25163) and Phase 2(NP22657) data,

[b] F1 for Phase 1PK/PD (NP25163) and Phase 2(NP22657) data starting Cycle 5 and after, and all Phase 3 (NO25026) cycles.

Figure 17.

Relationship between Statistically Significant Covariates Retained in the Final Population PK Model and Individual Estimated PK Parameters (NP25163, NP22657, and NO25026)



- The population half-life was estimated to be 2.15 days (51.6 h) and the accumulation ratio for a twice daily regimen was estimated to be 6.72 for the population. The primary individual PK parameters estimated for the 458 patients included in the population PK analysis are also used to derive individual secondary PK parameters half-life, accumulation ratio, steady state AUC, steady state C_{max} and steady state C_{min}. Summary statistics of the individual secondary PK parameters derived are summarised in Table 17. PK parameter relationships between gender and steady state AUC, C_{max} and C_{min} for the 960 mg regimen are shown in Figure 18.

Table 17.

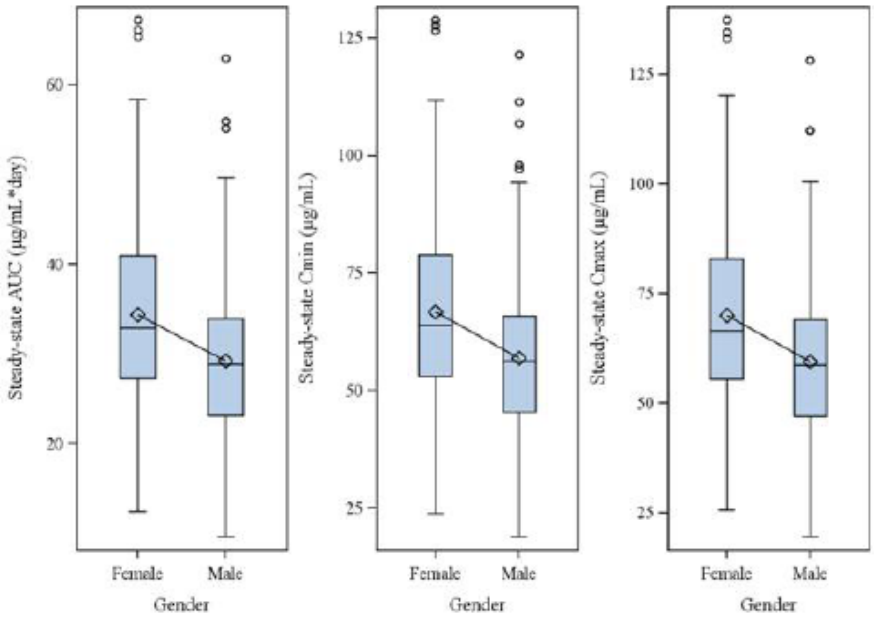
Secondary PK Parameters Derived Using the Primary Individual PK Parameters Estimated by the Final Population PK Model (NP25163, NP22657, NO25026)

Secondary PK Parameters	Mean	SD	Median	5th Percentile	95th Percentile
$T_{1/2}$ (day)	2.72	1.94	2.37	1.24	4.98
R_{acc}	8.36	5.60	7.36	4.10	14.9
$AUC_{ss,12h}$ (µg/mL·day)	31.4	9.42	30.6	17.5	47.9
$C_{ss,max}$ (µg/mL)	63.8	19.2	62.4	35.4	97.4
$C_{ss,min}$ (µg/mL)	61.0	18.3	59.1	34.1	93.5

$T_{1/2}$ = Half-life; **R_{acc}** = Accumulation ratio; **$AUC_{ss,12h}$** = Steady-state AUC; **$C_{ss,max}$** = Steady-state C_{max}; and **$C_{ss,min}$** = Steady-state C_{min}.

Figure 18.

Relationship between Gender and Secondary PK Parameters Steady-State AUC, C_{max}, and C_{min} (960 mg bid) Derived Using the Final Population PK Model



Effective intrinsic factors on the pharmacokinetics of VEM

Effective gender, body weight, BMI and age:

Assessment of the above parameters on VEM exposure was conducted in Study NP22657 using non compartmental analysis (NCAs). It was found that there was no clear relationship between VEM exposure ($AUC_{0\text{-}8\ h}$ on Day 15) either in body weight, body mass index or age, either in the overall population or the gender sub groups. However mean VEM exposure was approximately 42% higher in females than males as indicated in Table 18 and Figure 19. Similar results were seen for C_{max} on Day 15. This difference maybe attributed in part to the differences in the number of male versus female patients being approximately two thirds female.

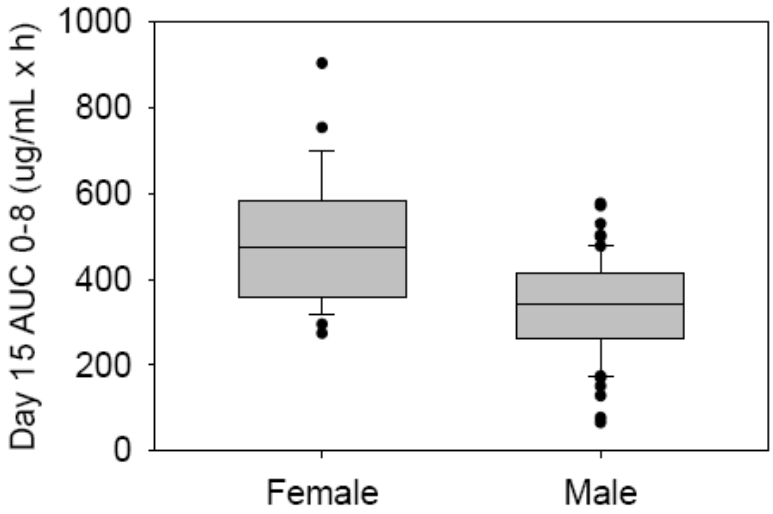
Table 18.

NP22657: Day 15 RO5185426 Exposure ($AUC_{0\text{-}8h}$ on Day 15) in Male and Female Patients (Primary PK Population)

	N	Mean ± SD (CV%) (µg·h/mL)	Median (µg·h/mL)	Min–Max (µg·h/mL)
Female	27	478.07 ± 151.20	476.30	273.84–903.93
Male	60	336.11 ± 116.64	340.73	66.22–576.60

Figure 19.

NP22657: RO5185426 Exposure ($AUC_{0\text{-}8h}$ on Day 15) in Male and Female Patients (Primary PK Population)



Effective extrinsic factors on the pharmacokinetics of VEM

Study NP22676 which was an open label multicentre Phase I study to evaluate the effect of VEM on the PK of five CYP450 substrates given as a drug cocktail has been discussed above.

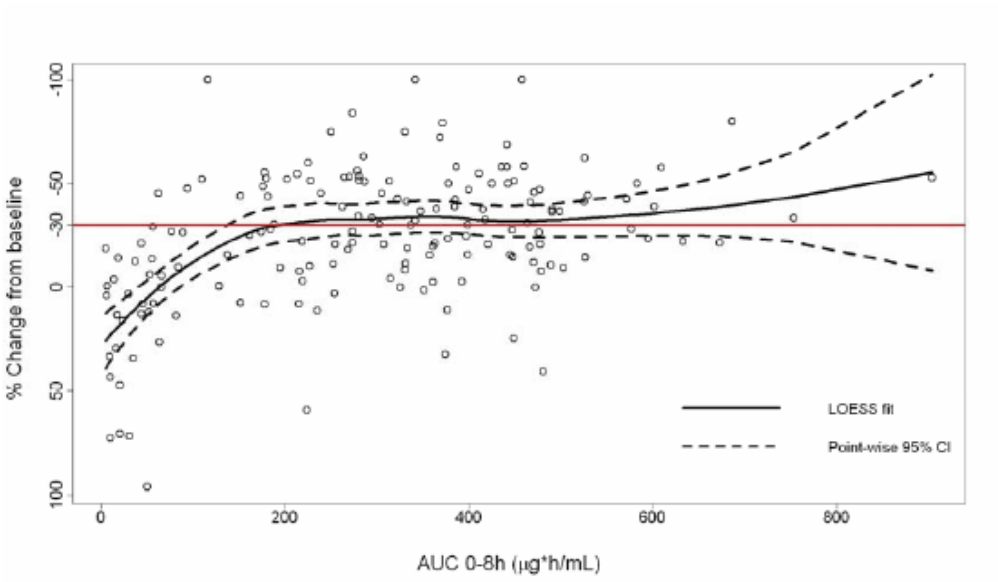
Exposure/efficacy relationship

Exposure and efficacy relationships were assessed by preliminary and exploratory analysis by NCA using clinical results from Studies NP22657 and PLX06-02 and by population PK/PD analyses using results from NP22657 and N025025.

The percent change from baseline in the RECIST measurements of tumour size taken from target tumours from patients in PLX06-02 and NP22657 served as a suitable quantitative measure for comparison with PK parameters. The 30% reduction from baseline and tumour size by RECIST criteria represented a cut-off for clinically meaningful reduction in tumour size with VEM treatment. Due to this exploratory analysis VEM exposure measured as $AUC_{0\text{-}8\ h}$ on Day 15 was chosen as a common PK parameter between the two studies. The effect of VEM on tumour size was generally measured on Day 43 but was correlated with the $AUC_{0\text{-}8\ h}$ measured on Day 15 in the exploratory analysis. Figure 20 depicts a graphic representation of the percent change from baseline in the first RECIST measurement of tumour size versus VEM exposure ($AUC_{0\text{-}8\ hours}$) on Day 15. The apparent increase in the reduction in tumour size measured by RECIST occurred with increasing VEM exposure up to approximately 200 µg.hr/ml. Above this exposure level it was difficult to ascertain a positive relationship between the effect size and VEM exposure. Of note consistent and more pronounced clinical tumour regression including at metastatic sites was observed at doses >720 mg twice daily.

Figure 20.

Percent Change From Baseline of First RECIST Measurement Compared with RO5185426 Exposure ($AUC_{0\text{-}8h}$) on Day 15 (PLX06-02 and NP22657)



In absence of an exposure/response relationship for reduction in tumour size by RECIST in the range of VEM exposures with 960 mg twice daily was observed in the separate analysis of data from NP22657.

A further analysis of mean VEM plasma exposures on Day 15 in patients with primary clinical endpoints of tumour response being partial response (PR), complete response (CR), stable disease (SD) and progressive disease showed no clear exposure response relationship across the range of exposures attained in 960 mg dose level.

In summary using the exposure data derived by NCA and exposure/response relationship is evident lower than exposures and appears to plateau with increasing exposure. Based on this analysis the VEM dose of 960 mg twice daily would provide VEM exposure to exhibit a clinically meaningful reduction of tumour size.

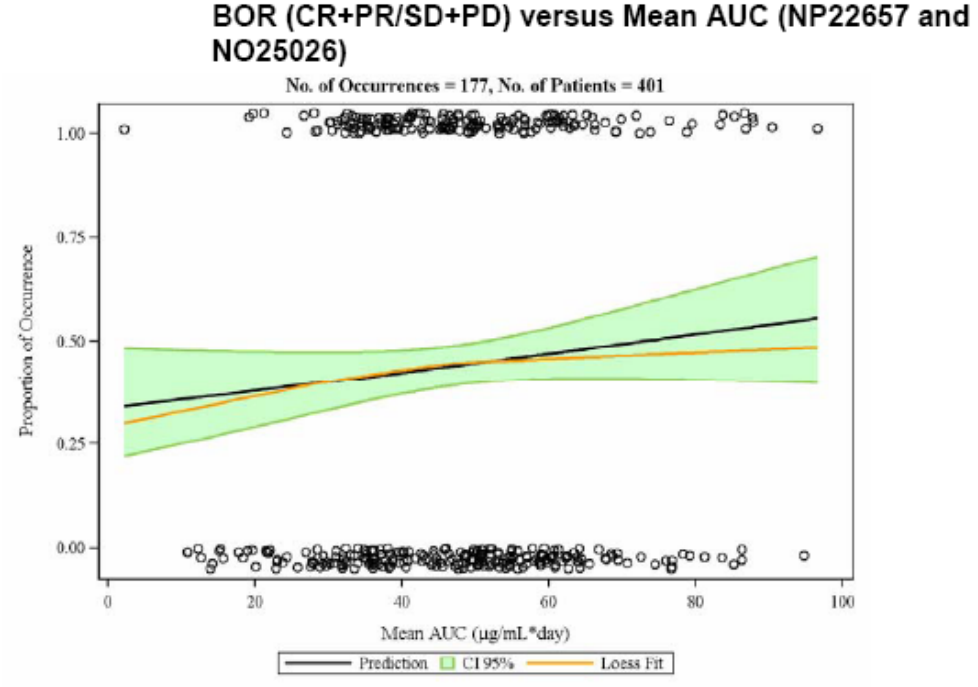
Exposure/efficacy relationship in the population PK/PD study

The main objectives of these analyses were to characterise the exposure/efficacy relationship for VEM using graphic analyses and to investigate whether the variability and response could be attributed to variability in VEM exposure.

Efficacy data from the Phase II NP22657 and Phase III NO25026 patients, who were included in the population PK analyses, were assessed. The relationship between the mean AUC and the mean efficacy parameters for changes in tumour size from baseline at the end of treatment and the best overall response, overall survival and PFS were analysed.

Significant reductions in tumour size over time were observed in all exposure categories. However, in the lower exposure category the percentage of patients with a positive increase in tumour size from baseline at the end of treatment was found to be higher (22%) than at the median and high exposure categories (being 11 and 9% respectively). These results indicated that the effect of VEM on tumour size could potentially increase in some patients if their exposure level goes above the low exposure category. This exposure/response relationship was found to be more pronounced in Phase II than Phase III as the percentage of patients with a positive increase in tumour size from baseline changed from 26%, 12% and 6% in the low, medium and high exposure category respectively versus 19%, 10% and 10% in the respective exposure categories for Phase III. Exposure effect observed in the change of tumour size with time is also apparent in the best overall response with a slight increase in the probability of getting PR or CR with increasing exposure. This is illustrated in Figure 21.

Figure 21.



Exposure/safety relationship

Exposure/safety relationships have been explored by the NCA utilising results from Study NP22657 and by population PK/PD analyses using results from Studies NP22657 and NO25025. The safety endpoints evaluated with treatment emergent adverse events of at least Grade III liver function tests results of at least Grade III and cuSCC.

In Study NP22657 the mean VEM exposures ($AUC_{0\text{-}8\ hours}$) was not substantially different between patients with or without AE of at least Grade III, liver laboratory abnormalities of at least Grade III or cuSCC.

Graphic analyses showed that there was no apparent effect of VEM exposure on the occurrences of ALT, AST, GGT and total bilirubin elevation. There was also no apparent effect of VEM exposure on the severity or time to first event for the liver laboratory abnormalities. For cuSCC there was a weak association between high exposures and higher occurrences of first event. However there was no apparent effect of VEM exposure on time to first event for the skin toxicities.

Evaluator comment

These PK analyses have demonstrated relevant determinants of parameters in relation to distribution, metabolism and excretion. Data in relation to bioavailability is not present on the basis that VEM is highly insoluble and therefore not amenable to development of IV formulations which would allow for determination of absolute bioavailability.

The only data not available in the current PK presentation relates to food effect. A study is presently underway to evaluate this and results will certainly be published and presented.

Pharmacodynamics

There were no specific data provided from human studies in this submission in relation to PD.

Dosage selection for the pivotal studies

Selection of the VEM dose used in the Phase II and Phase III clinical trials were based on nonclinical data and the clinical efficacy and safety observed in the Phase I Study PLX06-02.

Nonclinical *in vitro* evidence demonstrated self destruction only at lower VEM concentrations and apoptosis only at higher concentrations. Similarly in xenograft models, tumour stasis was observed at lower VEM concentrations and tumour shrinkage observed only at higher VEM concentrations >400 µg/hr. No exposure plateau was detected in the xenograft models and higher VEM concentrations were associated with greater tumour shrinkage and longer duration of survival. These findings suggested that VEM exposures in patients would need to exceed $AUC_{0\text{-}24\ h}$ >400 µg.h/mL to observe tumour regression. Furthermore it was considered more heterogeneity in tumour response and treatment with VEM depending on the tumour cell line used. Plasma VEM exposure >2000 µg.h was required for xenograft of tumour growth inhibition of some tumour cell lines. Therefore, the goal of the Phase I study was to use the highest dose of VEM that could be tolerated in order to maximise the therapeutic index for metastatic melanoma.

In the dose escalation phase of PLX06-02, which is based on a modified 3+3 accelerated titration design, the dose range of 160 mg to 1120 mg twice daily was evaluated with the optimised MBP formulation in this study. Consistent with the nonclinical findings, tumour regressions in Study PLX06-02 were first observed in the dose range of 240 mg twice daily to 360 mg twice daily, which exceeded the target exposure threshold of $AUC_{0\text{-}24\ h}$ >400 µg.h/mL and became more pronounced at higher doses. Early tumour responses were detected in patients with Stage M1A disease whereas disease in other patients in these initial dose cohorts progressed. Consistent and more pronounced tumour regression, including various metastatic sites was observed in the dose range of 720-1120 mg twice daily. However, DLTs primarily Grade III rash and Grade III fatigue were observed in four patients at 1120 mg twice daily indicating this dose could not be tolerated. Therefore, the maximum tolerated dose (MTD) of 960 mg twice daily representing the approximate mid-point between 720 mg and 1120 mg twice daily was selected for further clinical

development. In agreement with global health authorities, 960 mg twice daily was subsequently considered the appropriate dose for the Phase II and Phase III studies.

Efficacy

Clinical efficacy data to support the use of VEM for the treatment of patients with $BRAF^{V600}$ mutation positive unresectable or metastatic melanoma comes from three studies. These include the pivotal Phase III study of previously untreated patients (NO25026); a supportive Phase II study of previously treated patients (NP22657) and a supportive Phase I study (PLX06-02) consisting of an initial dose escalation phase in multiple tumour types and an extension phase in which metastatic melanoma and CRC patients were enrolled. All patients enrolled in the efficacy phase of these three clinical trials were selected using the companion diagnostic tests; either at an early prototype test in the PLX06-02 extension phase or the cobas 4800 BRAF V600 Mutation Test, which is the proposed commercial platform which was also used in the Phase II and Phase III studies. All three studies were multicentre international and open label with the pivotal Phase III Study NO25026, a randomised active treatment control study in previously untreated patients with unresectable Stage IIIC or Stage IV melanoma. The supportive Phase II Study NP22657 was a single arm uncontrolled clinical trial conducted in patients with Stage IV melanoma and disease which was refractory to at least one prior systemic therapy. The supportive Phase I Study PLX06-02 was a single arm uncontrolled clinical trial conducted in patients with metastatic cancer. Of the 32 patients in the metastatic melanoma cohort evaluated for this efficacy assessment, 24 of these patients were previously treated for metastatic melanoma.

Key study design features

Key inclusion criteria

Apart from differences in treatment history for metastatic melanoma key eligibility criteria for the pivotal supportive studies were similar. Patients were excluded from the studies if at screening they had any active central nervous system lesions, a history of carcinoma meningitis, a recent severe haemorrhage or a mean QTc interval of >450ms. Pregnant or lactating women were also excluded from the study.

Tumour assessments

Tumour responses were assessed by study investigators in Studies NO25026 and PLX06-02 and by an independent review committee (IRC) and by the Study investigator of the Study NP22657. The Response Evaluation Criteria In Solid Tumours (RECIST) was used in all studies.

Overall survival (OS) was defined as the time from randomisation in Study NO25026 or first treatment for the other two studies to death from any cause. In all studies 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.

Progression free survival (PFS) was defined as the interval between randomisation for Study NO25026 or as first treatment in Studies NP22657 and PLX06-02 and the data of progression, based on the actual tumour assessment date or death for any cause whichever occurred first. Best overall response rate (BORR) for the studies were defined as complete response or partial response. This response was assessed by RECIST. All responses for CR or PR were confirmed at the next tumour assessment. Patients who did not have any post baseline tumour assessment were considered as non-responders.

Duration of response was defined as the interval between the date of the earliest qualifying response and the date of progressive disease or death from any cause. This was calculated only for patients who had a best overall response to CR or PR.

All these above endpoints were assessed statistically by chi-square tests stratified log-rank tests and Kaplan-Meier curves.

Pivotal study NO25026

This randomised open label controlled multicentre Phase III study was conducted in a total of 104 centres including US, Europe, Canada, New Zealand and Australia. The first patient was randomised to trial on 4 January 2010, with 30 December 2010 as the clinical cut-off date for final evaluation. A total of 680 patients were planned to be enrolled in this study. Patients were randomised at a 1:1 ratio to either oral VEM administered twice daily at a dose of 960 mg or the control arm of Dacarbazine administered IV at 1000 mg/m^2 on Day 1 every three weeks. Patients were to continue on therapy until disease progression, treatment withdrawal or patient withdrawal.

Primary analyses for the assessment the two primary co-endpoints OS and PFS were performed for the per protocol population as exploratory analyses.

A total of 675 patients were randomised; 337 to the VEM group and 338 to the dacarbazine group. Baseline characteristics were well balanced between the two groups. Ninety-nine percent of the patients recruited to the study were White with a median age of 53-55 years with slightly more men (56%) than women (44%).

Baseline disease characteristics in the treatment groups were well balanced with respect to all stratification factors including each of the four disease stage classifications, lactose dehydroxygenase (LDH) at baseline and baseline ECOG performance status. The majority of patients had M1C stage disease and LDH was elevated in 42% of patients in both treatment groups.

With respect to disposition of patients, with the majority of patients in all studies discontinued VEM treatment because of progression of disease with a low incidence of premature discontinuations related to safety.

The median duration of VEM treatment in the pivotal study was 3.09 months. The mean total daily dose was 1.67 g per day with a target dose of 1.9 g per day.

A summary of the main efficacy results of the pivotal study is given in Table 19.

Table 19.

NO25026: Summary of Main Efficacy Results of RO5185426 in Treatment-Naive Patients with *BRAF*^{V600} Mutation-Positive Melanoma

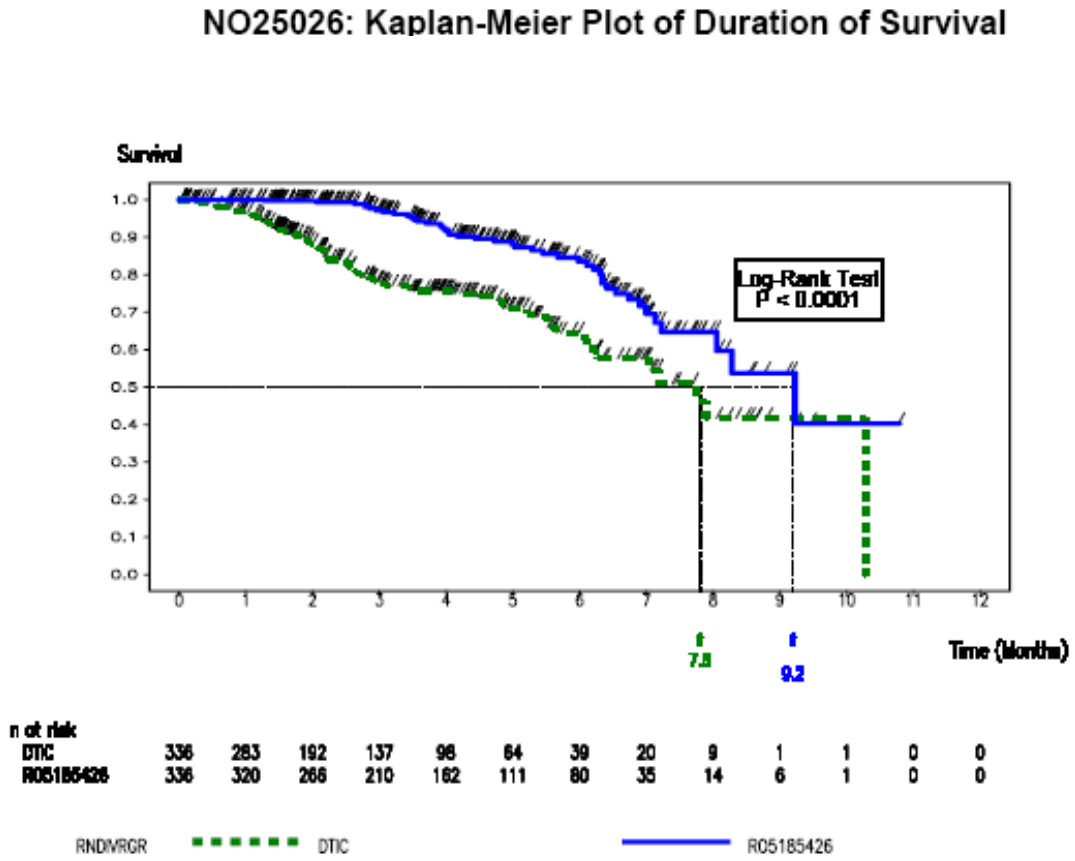
	DTIC	RO5185426
Overall survival (co-primary endpoint)		
Patients evaluable	336	336
Number of events	75	43
Hazard ratio	0.37	
95% CI	(0.26, 0.55)	
p-value (log-rank test, two-sided)	<0.0001	
6-month event-free rate	64%	84%
95% CI	(56%, 73%)	(78%, 89%)
Kaplan-Meier estimate of median (months) considered not reliable estimates at the time of this analysis (see CSR NO25026: 5.3.5.1.1/Vol.47/p.91)	7.75	9.23
95% CI	(6.28, 10.28)	(8.05, not reached)
Median duration of follow up (months)	2.33	3.75
Range	<0.1 to 10.3	0.3 to 10.8
PFS (co-primary endpoint)		
Patients evaluable	274	275
Hazard ratio	0.26	
95% CI	(0.20, 0.33)	
p-value (log-rank test, two-sided)	<0.0001	
6-month event-free rate	12%	47%
95% CI	(7%, 18%)	(38%, 55%)
Kaplan-Meier estimate of median	1.61	5.32
95% CI	(1.58, 1.74)	(4.86, 6.57)
Best overall response (secondary endpoint)		
Patients evaluable	220	219
Response rate (confirmed)	12 (5.5%)	106 (48.4%)
95% CI	(2.8%, 9.3%)	(41.6%, 55.2%)
p-value (Chi-squared test)	<0.0001	
Duration of response (secondary endpoint)		
Number of responding patients	12	106
Kaplan-Meier estimate of median	Not reached	5.49
95% CI	(4.60, not reached)	(3.98, 5.72)

	DTIC	RO5185426
Time to Response (secondary endpoint)		
Number of responding patients	12	106
Median (months)	2.72	1.45
Range	1.6 to 5.8	1.0 to 5.5

Reviewing overall survival (a co-primary endpoint), the unstratified analysis for all randomised patients showed that the treatment with VEM demonstrated a clinically meaningful and statistically significant improvement in the duration of overall survival compared with dacarbazine treatment with a P value <0.0001 by the log rank test. The hazard ratio for death was 0.37 representing a 63% decrease in the hazard of death for patients in the VEM group compared with the patients in the dacarbazine group.

The Kaplan-Meier (KM) estimate of the proportional life at six months of patients in the VEM group was 84% whereas in the dacarbazine group it was 64%. The KM curves for overall survival depicted the KM estimate of the proportion of patients who were alive by time since randomisation in Figure 22. At the time of analysis, the KM estimate of median overall survival for the VEM group was 9.23 months with the upper limit of 95% CI not being reached, with six patients in follow up. For the dacarbazine group the median overall survival was 7.75 months with 10 patients in follow up.[21]

Figure 22.



A sub group analysis of pre treatment factors in relation to the influence overall survival revealed a treatment effect in favour of VEM clearly observed across all sub groups.

A sensitivity analysis of OS was performed in which the stratified log-rank test was performed and a stratified hazard ratio was calculated. Stratification factors included metastatic classification and ECOG performance status. Results were consistent with the results from the unstratified analyses, again with a P value of <0.0001 and a stratified hazard ratio of 0.36.

[21] Sponsor comment: "KM estimates of median OS for VEM and dacarbazine were considered not reliably estimated at the time of this analysis because few patients had >7 months follow-up."

Reviewing progression free survival (PFS) which is a co-primary endpoint, the final analysis of PFS was performed as planned at the time of the interim analysis OS. Among the 549 patients evaluable for analysis of PFS (the ITT population), a total of 286 patients had died or experienced disease progression at clinical cut-off being 104 patients in the VEM group and 182 in the dacarbazine group, as indicated in Table 20, unstratified analysis of PFS demonstrated statistically significant increase in PFS in favour of the VEM group with a P value of <0.0001 by log rank test. The unstratified hazard ratio for progression or death for VEM relative to dacarbazine was 0.26. This represented a 74% decrease in the hazard of progression or death in the VEM group compared with the dacarbazine group. The KM estimate of median PFS for patients in the VEM group was 5.32 months where as in the dacarbazine group it was 1.61 months as indicated Figure 23. At six months, the KM estimate of the percentage of patients who were progression free in the VEM group was 47% as compared to 12% in the dacarbazine group.

Table 20.

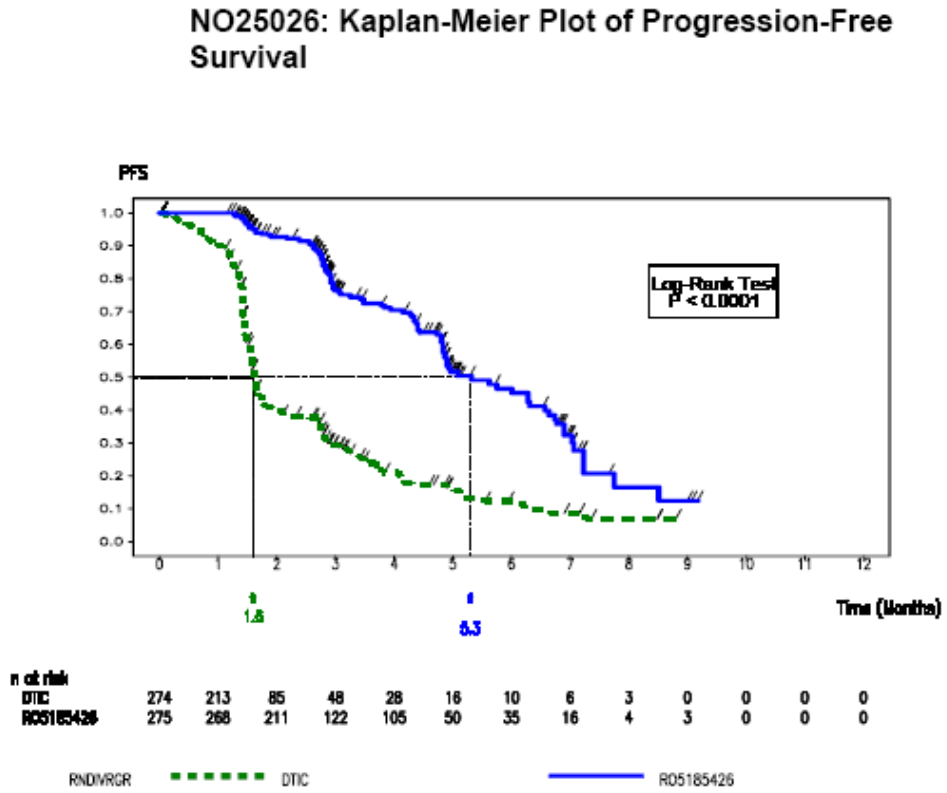
NO25026: Progression-Free Survival (Unstratified Analysis)

	DTIC (N=274)		RO5185426 (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]

Time to event1 (months) variable is PFSTMM, Censoring variable is CSPFS (0 = censored, 1 =event)
Clinical cut off date is Dec 30,2010.
The population evaluable for PFS is defined as all patients randomized by Oct 27, 2010.

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 23.



Sub group analysis of PFS revealed a treatment effect in favour of VEM across all sub groups.

The robustness of the PFS analysis was confirmed by performing a sensitivity analysis in which a stratified log rank test and a stratified hazard ratio were calculated compared to those in the unstratified analysis. PFS benefit estimated for the stratified analyses of PFS was consistent with the unstratified analysis again; P <0.0001 with a hazard ratio of 0.22.

Reviewing best overall response (a secondary endpoint), a total of 439 patients (219 patients in the VEM group and 220 in the dacarbazine group) were randomised at least 14 weeks prior to clinical cut-off date and were therefore evaluable for analysis of confirmed BORR. A total of 106/219 patients in the VEM group and 12/220 in the dacarbazine group had a response that was confirmed. The confirmed response rate in the VEM group was 48.4% whereas in the dacarbazine group it was 5.5% with a P value of <0.0001 as indicated in Table 21. Two of the patients in the VEM group had a CR. Sub group analysis revealed a treatment effect on confirmed BORR in favour of VEM treatment across all sub groups examined.

Table 21.

Ta NO25026: Best Overall Response (Confirmed)

t_respl_EVALBORC Table 14.2/7 Best Overall Response (Confirmed)
PRotocol(s): NO25026
Analysis Population: Patients Evaluable for BORR

	DTIC (N=220)		RO5185426 (N=219)
Responders[a]	12 (5.5 %)		106 (48.4 %)
Non-Responders	208 (94.5 %)		113 (51.6 %)
95% CI for Response Rates[b]	[2.8; 9.3]		[41.6; 55.2]
Difference in Response Rates		42.95	
95% CI for Difference in Response Rates[c]		[35.4; 50.5]	
p-Value (Chi-squared Test w. Schouten Corr.)		<.0001	
Odds Ratio		16.26	
95% CI for Odds Ratio		[8.58;30.81]	
Complete Response (CR)	0 (0.0 %)		2 (0.9 %)
95% CI for CR	[0.0; 1.7]		[0.1; 3.3]
Partial Response (PR)	12 (5.5 %)		104 (47.5 %)
95% CI for PR	[2.8; 9.3]		[40.7; 54.3]
Stable Disease (SD)	53 (24.1 %)		81 (37.0 %)
95% CI for SD	[18.6; 30.3]		[30.6; 43.8]
Progressive Disease (PD)	103 (46.8 %)		23 (10.5 %)
95% CI for PD	[40.1; 53.6]		[6.8; 15.3]
Missing (No Response Assessment)	52 (23.6 %)		9 (4.1 %)

Best Confirmed Overall Response (variable BORESP)
Clinical cut off date of Dec 30,2010.
The population evaluable for BORR is defined as all patients randomized by Sept 22, 2010.

a. Patients with best overall response of confirmed CR or PR
b. 95% CI for one sample binomial using Pearson-Clopper method
c. Approximate 95% CI for difference of two rates using Hauck-Anderson method

Reviewing duration of response among the patients who had a confirmed overall response, the median duration of response was 5.49 months in the VEM group but was not reached in the dacarbazine group as indicated in Table 22. At the time of the analysis the duration response range of 1.22–7.62 months in the VEM group and 1.18-5.55 months in the dacarbazine group.

Table 22.

NO25026: Duration of Response among Patients with a Confirmed Response (Patients Evaluable for BORR)

t_dur_resp_conf_EVALBORC Table 14.2/8 Duration of Response (Confirmed)
Protocol(s): NO25026
Analysis Population: Patients Evaluable for BORR

	DTIC (N=220)		RO5185426 (N=219)
Patients included in analysis	12 (100.0 %)		106 (100.0 %)
Patients with event	2 (16.7 %)		30 (28.3 %)
Patients without events	10 (83.3 %)		76 (71.7 %)
Time to event (months)			
Median[a]	.		5.49
95% CI for Median[b]	[4.60;.]		[3.98;5.72]
25% and 75%-Quartile	4.60;.		3.68;6.60
Range[c]	1.18 to 5.55		1.22 to 7.62
p-Value (Log-Rank Test)		0.3619	

Time to event (months) variable is DURBORM, Censoring variable is CSDRESP (0 = censored, 1 =event)
Clinical cut off date is Dec 30,2010.
The population evaluable for BORR is defined as all patients randomized by Sept 22, 2010.
Patients with best overall response of confirmed CR or PR

a. Kaplan-Meier estimate
b. 95% CI for median using the method of Brookmeyer and Crowley
c. Includes censored observations

The time to response (a secondary endpoint in the study) was evaluated for patients with a confirmed response. Among the 106 VEM treated patients with a confirmed median time to response of 1.45 months with a range of 1-1.5 months and the majority of respondents, that is, 75% who responded to treatment with VEM by the time of the first post baseline treatment assessment. Among the 12 Dacarbazine treated patients, the median time to response was 2.72 months with a range of 1.6 – 5.8 months. The majority of responders (75%) who had responded to treatment with dacarbazine by the time of the second post baseline assessment being 3.2 months.

Reviewing patient reported outcomes: The functional assessment of therapy consisted of four general health sub scales including physical wellbeing, social wellbeing, emotional wellbeing and functional wellbeing (FAC-M). Analyses of FAC-M suggested that quality of life over time during study treatment differed little between treatment groups.

Similar results were obtained in relation to analysis of pain scores reported by the patient using linear analogue scales. This suggested that there was no difference in pain scores measured over time on study between treatment groups.

For physical symptom improvement outcomes, the data obtained suggested that the proportion of patients with improvement in the use of concomitant narcotic analgesics was higher in the VEM group (12.9%) than the dacarbazine group (4.5%). There was no evidence that there was any difference between treatment groups in the proportion of patients who showed an improvement in oxygen saturation. Physician assessment of performance status noted that 53.4% of patients on VEM therapy obtained an improvement in performance status as compared to 20.2% of patients receiving Dacarbazine.

Evaluator Comment:

The data from this quite large Phase III well conducted randomised trial very clearly show a significant benefit in terms of all primary and relevant secondary endpoints; namely

overall survival, progression free survival and overall response rate. Sensitivity and sub group analyses confirmed the significant benefits for VEM in comparison to the previous standard therapy, dacarbazine. These data would indicate a significant therapeutic advance in the treatment of metastatic melanoma which is notoriously resistant to available therapies.

Supportive Phase II Study NP22657:

The key demographic features of the study were generally similar to those seen in the pivotal trial. Similar to the pivotal trial, the majority of patients had M1c disease (61%), normal LDH level at baseline (51%) and an ECOG performance status of 0 and 1.

The majority of patients who discontinued treatment did so because of progressive disease. The extent of exposure to VEM treatment in the study was 5.67 months [22]. The mean total daily dose was 1.61 g per day.

Reviewing the overall survival data for Study NP22657 (a secondary endpoint). At the time of clinical cut-off of 27 September 2010, the median overall survival had not been reached, with the range for duration of survival being 0.6–11.3 months. A KM estimate of this 6 month survival was 77%. At the time of analysis the median duration of follow up was 6.87 months with a range of 0.59–11.27 months.

The median PFS was (as assessed by the RIC) 6.1 months ranging from 0-10.2 months.

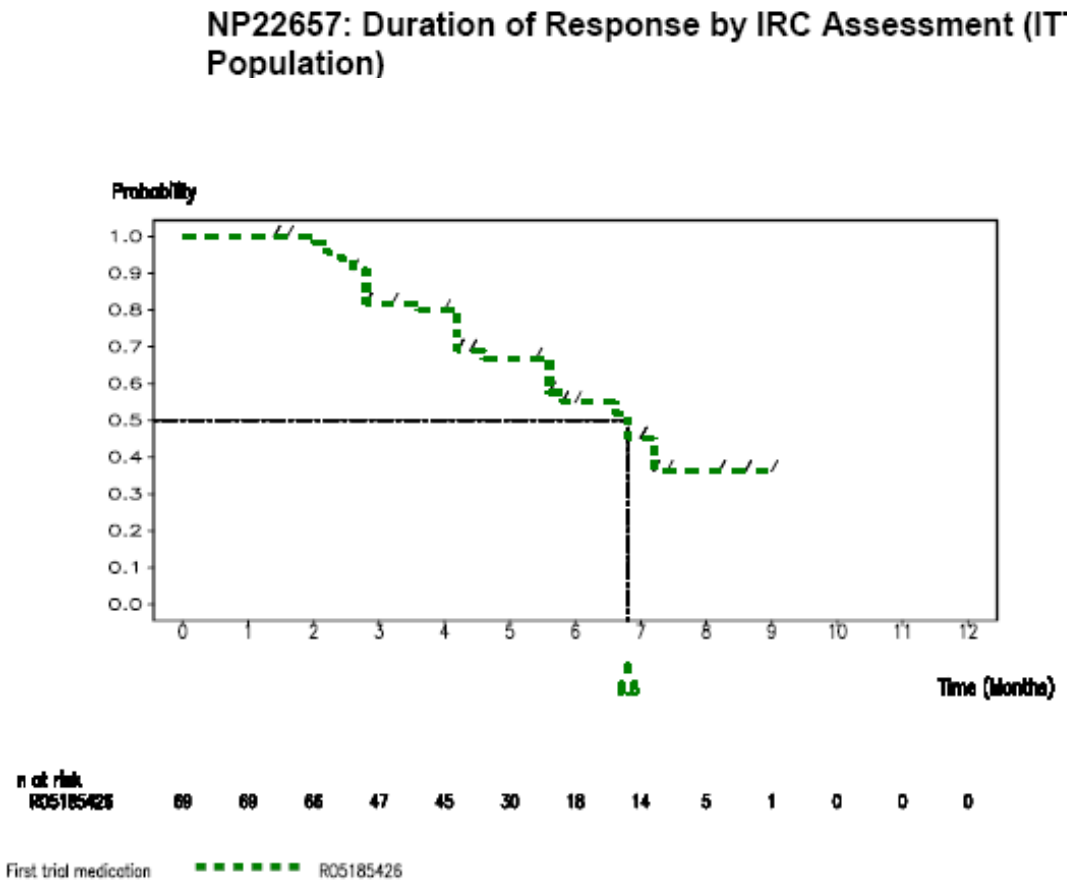
In relation to best overall response rate (the primary efficacy variable for this study) as assessed by the IRC according to RECIST criteria. There were 69 responders with a confirmed complete or partial response among the 132 patients, for an overall response rate of 52.3%. Among the 69 responders there were three CRs (2.3%) and 66 PRs (50%).

Review of sub group analysis revealed that in relation to the key prognostic factors of LDH, ECOG performance status and stage, these were consistent with overall data. However, for patients with an LDH value of >1.5 times the upper limit of normal among 46 patients in this sub group the overall response rate was 33%. Similarly, for patients who received prior treatment with Ipilimumab or Temelimumab (7 patients) the response rate was 28.57%. These data also essentially confirmed when reviewing overall response rate as assessed by the investigator with an overall response of 55% including four CRs. Efficacy in the sequence $BRAF^{V600}$ sub group was consistent with the efficacy in the ITT population selected by the cobas test. Of the 97 patients whose $BRAF^{V600}$ mutation was detected by Sanger frequency, the overall response rate was 57% with three CRs.

Reviewing duration of response by IRC assessment, the median duration response was 6.5 months with a range of 1.4–9 months (Figure 24).

[22] Sponsor comment:" 5.67 is the median".

Figure 24.



In relation to time to response as assessed by the IRC, this was 1.4 months with a range of 1.2–5.5 months. The majority of responders had responded to treatment at the first baseline[23] tumour assessment after 1.6 months.

In relation to patient reported outcomes; for the FACT-M scores there was no discernible trend observed. Similarly there was little change in the visual analogue scores for the study in relation to pain. Improvement in the global performance status was shown in 83.8% of patients in the mean time to maximum global performance improvement of eight weeks. Mean improvement was over two levels.

Evaluator comment:

These data have therefore again shown a significant benefit for the use of VEM in the treatment of patients with metastatic melanoma with a higher response rate than has been previously observed for standard therapies. Similarly, several patients achieved complete response which is a very uncommon outcome in metastatic melanoma. These data therefore confirm the robust result from the pivotal trial.

[23] Sponsor comment: "The majority of responders had responded to treatment at the first *post*-baseline tumour assessment of 1.6 months".

Supportive Phase I Study PLX06-02

This was a melanoma extension phase of Phase I study involving 32 patients. Again, the majority of patients in this trial were White.

The most common ECOG status was status 1 in 56.3% of patients with a median time since last progression of disease of 1.41 months. The vast majority of patients had received prior treatment for metastatic disease.

The majority of patients who discontinued therapy did so because of progression of disease.

The median duration of treatment with VEM in the study was 8.83 months.

Reviewing the overall survival in this melanoma extension cohort including only those patients with $BRAF^{V600}$ mutation positive metastatic melanoma treated with 960 mg of VEM twice daily; the median overall survival was not reached with a KM estimate of the one year overall survival at 56.8% (Figure 25).

In relation to progression free survival (a secondary efficacy endpoint in this study), the KM estimate of the median PFS was 7.8 months. The KM estimate of the proportion of patients who were alive and progression free at six months was 59%. After one year it was 17%.

In relation to sub group analysis in the previously treated sub population, the melanoma extension cohort patients being 24 patients, the median PFS was 7.8 months which was consistent with that for all patients.

In relation to best overall response, the objective response rate was the primary efficacy measure in this study; a total of 18 evaluable patients in the melanoma extension cohort had a confirmed response with an overall response rate of 56.3% including three CRs and 15 PRs.

In relation to duration response, the median duration of response was 7.6 months with a range of 88->337 days, whereas the median time to response was 56.5 days with a range of 25-168 days.

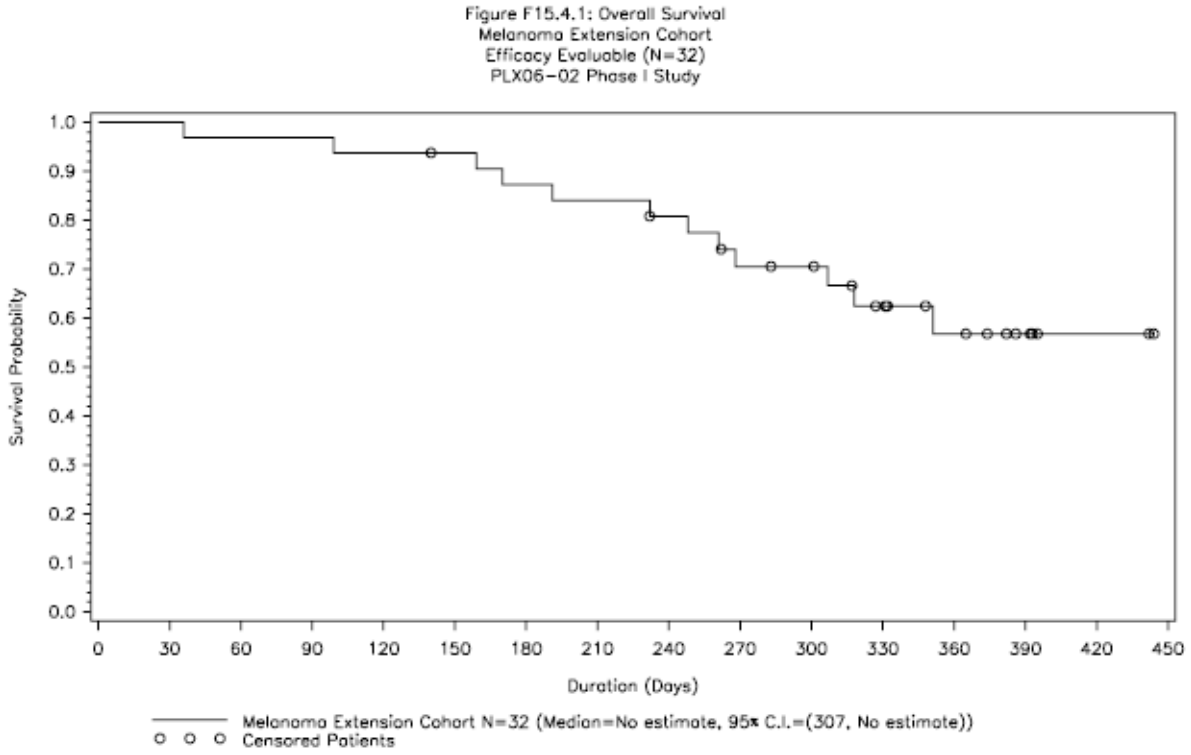
Evaluator comment:

Once again these data have demonstrated significant evidence of benefit in terms of response and progression free survival indicative of a level of efficacy for VEM superior to that observed with the previously available therapies for metastatic melanoma.

The three studies have clearly shown levels of efficacy superior to that previously seen, representing a potentially significant advance in the management of advanced stage melanoma.

Figure 25.

PLX06-02: Kaplan-Meier Plot of Overall Survival – Melanoma Extension Cohort (Efficacy Evaluable Population)



Overall Survival is calculated from date of first study drug until censoring or date of death. For patients without evidence of death at the time of the analysis; study termination, analysis cutoff, or start of confounding anticancer therapy, Overall Survival will be the calculated difference from the date of first study drug administration until the last known alive date from the Follow-up CRF. These patients will be censored in the analysis. For patients without follow-up, the overall survival will be the calculated difference from the date of first study drug administration until the last record patient visit. These patients will be censored in the analysis.
Cross-Reference: Appendix Listing 16.1.34

Safety

Introduction

A total of six studies are provided in this submission for assessment of clinical safety including the pivotal Phase III Study in NO25026, the Phase II Study NP22657 and the melanoma extension cohort of the Phase I Study PLX06-02. Also included are data from three pharmacologic Studies NP25158, NP22676 and NP25163.Overall the safety population included a total of 866 patients who received at least one dose of study drug, including VEM 584 patients and DTIC 282 patients.

Inclusion criteria for these six studies have been previously described. The exclusion criteria were comparable among the six studies.

Adverse events were monitored continuously throughout the studies and reported according to NCI criteria using the accepted 5-point scale. Laboratory assessments included haematology, serum biochemistry, urine analysis and vital signs; blood pressure, temperature, pulse, respiratory rate and weight together with ECGs and findings on physical examination.

For all six studies, if dose modifications, interruptions or delays were required these were undertaken according to established criteria. When it was determined that cutaneous SCCs were adverse effects associated with VEM administration, subsequent patients entered onto all studies underwent regrowth dermatological assessments. Recurrence of cutaneous SCCs was classified as a Grade III event. A proportion of patients in the extension Phase I Study PLX06-02 and Phase II Study NP22657 who developed cutaneous SCCs had these lesions assessed by molecular characterisation of biopsy samples.

Patient disposition

Pivotal Phase III Study NO25026:

The safety population was defined as all treated patients who had at least one on-study assessment. Of the 625 patients enrolled and treated, 618 were included in the safety population, 336 treated with VEM and 282 treated with dacarbazine. Of the 618 patients in this population who received treatment with VEM or Dacarbazine, 113 (34%) treated with VEM and 200 (71%) treated with dacarbazine were prematurely withdrawn at time of clinical cut-off. The most common reason for discontinuation of treatment was disease progression.

Pooled safety population for Phase I PLX06-02 and Phase II NP22657

Of the 164 patients who received treatment with VEM, 63% were prematurely withdrawn at time of clinic cut-off for each study; 22 patients from the Phase I study and 82 from the Phase II study and 91% of these had progressive disease.

Supporting clinical pharmacology studies

Overall a total of 84 patients were enrolled, received treatment with VEM and were evaluable for safety in the three clinical pharmacology studies. Of these 84 patients, 19 were prematurely withdrawn, 15 of these due to progressive disease.

Overall extent of exposure

Pivotal Phase III Study NO25026

As of the clinical cut-off date for the Phase III study, the median total cumulative VEM dose was 195 g as compared to dacarbazine where it was 2000 g/m^2. The duration of treatment in the VEM group was 3.1 months as compared to 0.6 months in the dacarbazine group. The median total daily dose of VEM was 1.87 g per day and the median dose densities,

defined as the total actual dose taken divided by the total planned dose between date of first and last dose, was 97.6% for the VEM group.

Reviewing dose modifications for the VEM treated patients: Of the 336 patients in the VEM group, 47% had a dose modification for any reason, of which 112 had at least one dose reduction with a mean number of dose reductions per patient of 1 and this is indicated in Table 23. A total of 147 patients (44%) had a dose interruption, with the number of interruptions being two for a mean of eight days. A total of 129 patients (38%) had a dose modification or interruption because of an adverse event of which the most common was Grade III rash in 24 patients. At least half of these resolved without sequelae and none led to discontinuation of study treatment.

Table 23.

Summary of Dose Modification (Reduction or Interruption) for Patients Receiving RO5185426 (Phase 3 [NO25026] Study, Safety Population)

	RO5185426 N=(336) n(%)
Patients with at least one dose modification (reduction or interruption)	
N(%)	159(47.3)
Dose modification Reasons:	
Dose adjusted per protocol	92(27.4)
Non-compliance	26(7.7)
Other	136(40.5)
Patients with at least one dose reduction	
N(%)	112(33.3)
Number of dose reductions per patient	
Mean	1
SD	0.6
Median	1
25% and 75%-ile	1-2
Min,Max	1-5
Last prescribed total daily doses for patients with dose reduction (mg per day)	
n	112(33.3)
1680 mg	1(0.3)
1440 mg	83(24.7)
1200 mg	1(0.3)
960 mg	26(7.7)
480 mg	1(0.3)
Patients with at least one dose interruption	
N(%)	147(43.8)
Number of dose interruptions per patient	
Mean	2
SD	1.1
Median	1
25% and 75%-ile	1-2
Min,Max	1-6
Duration of Maximum Dose Interruptions per patient (days)	
Mean	8
SD	6.2
Median	7
25% and 75%-ile	4-12
Min,Max	1-38
<1 Week	67(19.9)
>=1 Week	80(23.8)

NOTE: All percentages are based on N=336

* Per-protocol: Dose modification for safety reasons (see Section 1.1.2.3 for information on dose modification rules specified in the protocol).

** 80% of the reasons coded as "other" were because of an AE. The other 20% were a mixture of reasons including: missed dose, held dose, forgot to take drug, ran out of drug, drug holiday, progressive disease, patient decision, etc.

Phase I/Phase II studies in pooled safety population

The mean total cumulative VEM dose and duration of treatment for the pooled safety population was 319 g and 6.1 months respectively. The mean total daily dose was 1.36 g per day and the median dose intensities were 85% and 92% respectively. These were similar to those observed in the Phase III study.

In relation to dose modifications in the 164 patients in the pooled safety population, 43% had dose reduction for any reason of which 68% had one dose reduction and 30% two dose reductions. Some 94/154 patients (57%) had a dose interruption and the mean number of interruptions per patient was 2.6 with a range of 1-15. The most common reason for dose modification or interruption was an adverse event (involving 57% of instances) and the most common being Grade II or III rash. The majority of these rashes resolved without sequelae and none led to discontinuation of study treatment.

Supporting clinical pharmacology studies

Drug exposure for these three studies included in Study NP22676, which involved three treatment periods, the mean cumulative dose for VEM ranged from 0.26 months to 3.39 months. For Study NP25158, which involved seven patients, the median duration of exposure to VEM was 2.44 months with a mean cumulative dose of 138.58 g. For Study NP25163 the median duration of exposure to VEM was 64 days with a range of 15-189 days and a median cumulative dose of 92880 mg of VEM.

In relation to dose modifications in Study NP22676, eight patients experienced a total of 13 adverse events requiring dose modification; rash occurred in four patients (16%). In Study NP25158, one patient experienced Grade III fatigue requiring dose interruption, while in Study NP25163 seven patients had dose interruptions of 22 dose modifications, the most common relating to adverse event particularly skin rash.

Adverse events

Pivotal Phase III Study NO25026

An overview of adverse events in the Phase III study is provided in Table 24. Most patients in this study experienced at least one adverse event of any severity; 97% compared to 90% of patients on Dacarbazine; and 71% and 65% of patients receiving VEM and dacarbazine respectively experienced at least one adverse event that occurred within 28 days prior to discontinuation of study therapy.

The most commonly reported adverse events in the VEM group were in the System Organ Class (SOC) of Skin and subcutaneous tissue disorders, where 90% of patients had at least one adverse event which can be compared to 19% in the dacarbazine group. The most commonly occurring adverse event in this SOC were rash, alopecia and photosensitivity reaction. The next most common was Gastrointestinal disorders with similar overall incidences in the two groups of patients; 63% for VEM and 65% for Dacarbazine. Nausea, vomiting and constipation were more common in the dacarbazine group while diarrhoea was most common in the VEM group. Other adverse events occurring more commonly in the VEM patients included arthralgia, cutaneous SCC, keratoacanthoma, increased alkaline phosphatase and increased ALT. Other adverse events also occurring more frequently in VEM patients included skin papilloma, headache, dysgeusia, pyrexia, peripheral oedema, extremity pain, myalgia and decreased appetite. More common among the dacarbazine patients was neutropenia, vomiting and constipation. More patients in the VEM group (94%) than in the dacarbazine group (69%) had at least one adverse event that was considered by the study investigator to be related to treatment.

Table 24.

Overview of Adverse Events and Deaths (Phase 3 [NO25026] Study, Safety Population)

	Dacarbazine (N = 282)		RO5185426 (N = 336)	
Adverse Events	Number (%) of Patients			
Any AEs	253	(90)	326	(97)
Treatment-related AEs	194	(69)	316	(94)
AEs of Grade ≥ 3	86	(30)	168	(50)
Treatment-related AEs of Grade ≥ 3	53	(19)	143	(43)
Deaths†	66*	(23)	42*	(13)
Deaths within 28 days of last dose of study drug†	16	(5.5)	22	(6.5)
SAEs	45	(16)	110	(33)
Treatment-related SAEs	15	(5)	88	(26)
AEs that led to withdrawal from treatment	12	(4)	19	(6)
AEs that led to dose modification/interruption	44	(16)	129	(38)

* 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 fo RO5185426.

The most common adverse events of a Grade III or greater among VEM patients were SCC of skin (in 11%) and rash (in 8%), while the most common in Dacarbazine patients were neutropenia (in 9%) and decreased neutrophil count (in 4%). The greater percentage of patients in the VEM group (43%) and the dacarbazine group, that is, 19% experienced adverse events of Grade III or greater considered by the study investigator to be related to treatment. The most common treatment related adverse events of Grade III or greater were SCC of skin, rash and keratoacanthoma. These are illustrated in Table 25.

Table 25.

Summary of Treatment-related AEs of Grade ≥ 3 with an Incidence ≥ 2% in any Group (Phase 3 [NO25026], Safety Population)

ael3_gr34_scs Summary of Adverse Events NCI CTCAE Grade >= 3 with an Incidence >= 2%
Protocol(s): NO25026
Analysis: SAFETY Center: ALL CENTERS
Adverse Event Onset between Time of Very First Drug Intake and Study Day 9999, Time 23:59

Adverse Event	DTIC N = 282 No. (%)	RO5185426 N = 336 No. (%)
SQUAMOUS CELL CARCINOMA OF SKIN	1 (0.4)	38 (11.3)
RASH	-	28 (8.3)
NEUTROPENIA	24 (8.5)	1 (0.3)
KERATOACANTHOMA	-	20 (6.0)
ARTHRALGIA	2 (0.7)	11 (3.3)
DYSPNOEA	8 (2.8)	2 (0.6)
NEUTROPHIL COUNT DECREASED	10 (3.5)	-
GAMMA-GLUTAMYLTRANSFERASE INCREASED	-	9 (2.7)
PHOTOSENSITIVITY REACTION	-	9 (2.7)
RASH MACULO-PAPULAR	-	8 (2.4)
THROMBOCYTOPENIA	6 (2.1)	2 (0.6)
BLOOD ALKALINE PHOSPHATASE INCREASED	-	7 (2.1)

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
AE13 08MAR2011:18:19:07 (1 of 1)

With regards to Grade IV adverse events, the overall incidence was lower in the VEM group of patients (4%) compared to the dacarbazine group (8%). Grade IV events occurring in VEM patients included pulmonary embolism in three patients and increased GGT in two patients. The remaining Grade IV adverse events were singular in nature. In relation to the elevated GGT levels, these enzyme elevations settled in two patients upon interruption of therapy and the patients were able to return to treatment. The higher incidence of Grade IV events in the dacarbazine group principally related to neutropenia and thrombocytopenia. These were considered related to treatment.

Adverse events with a fatal outcome occurred with the same frequency in both treatment groups; six patients in each group. Only one of these was considered to be related to VEM treatment. It involved a patient with a cerebral metastasis that subsequently bled. It was not possible to completely exclude a treatment related effect.

Studies PLX06-02 and NP22657

An overview of the adverse events indicated that these were essentially similar to those observed in the Phase III trial and are summarised in Table 26. All patients in the pooled safety population experienced at least one adverse event of any grade and a total of 112 patients experienced at least one adverse event that occurred within 28 days prior to discontinuation of study therapy.

Table 26.

Overview of Adverse Events and Deaths (Phase 1 [PLX06-02]/Phase 2 [NP22657] Studies and Pooled Safety Population)

	Phase 1 Study PLX06-02 N (%)	Phase 2 Study NP22657 N (%)	Pooled Safety Population N (%)
No. of Patients	32	132	164
Patients with at least one AE	32 (100)	132 (100)	164 (100)
Treatment-related AEs	32 (100)	130 (98)	162 (99)
AEs of Grade ≥ 3	26 (81)	96 (73)	123 (75)
Treatment-related AEs of Grade ≥ 3	21 (66)	80 (61)	102 (62)
Deaths [a]	-	41 (31)	41 (25)
Deaths within 28 days of last RO5185426 dose	-	16 (12)	16 (10)
SAEs	18 (56)	67 (51)	85 (52)
Treatment-related SAEs	16 (50)	48 (36)	64 (39)
AEs leading to withdrawal from treatment	-	4 (3)	4 (2)
AEs that led to dose modification/interruption	20 (62)	74 (56)	94 (57)

[a] 39 were due to disease progression

The majority of patients (75%) in the pooled safety population experienced at least one adverse event of Grade III or greater. The most common of these were SCC of the skin (23%), elevated GGT (9%), arthralgia (7%), rash (7%), basal cell carcinoma (5%) and macular papilla rash (5%). Those considered related to VEM treatment were reported in 62% of patients and the most common was SCC of the skin (in 23%) and is indicated in Table 27. A total of 42 patients (26%) were diagnosed with cutaneous SCC. Other treatment related Grade III reactions included rash (6%), macular papilla rash (5%), red hand syndrome (2%), ethematous rash (1%) and generalised rash (<1%). Photosensitivity reactions were reported in six patients (4%). Elevations of GGT to at a least Grade III level were noted in 14 patients (9%), elevated bilirubin in 4% of patients, elevated ALT in 4% of patients, ALP in 2% of patients and AST in 2% of patients. Other symptoms of note related to VEM included arthralgia and fatigue in 5% and 2% of patients respectively. Four patients with >Grade III reactions discontinued treatment. One of these related to hepatic dysfunction and was considered related to therapy.

Table 27.

Summary of Treatment-related AEs of Grade ≥ 3 with an Incidence ≥ 2% in any Group (Phase 1 [PLX06-02]/Phase 2 [NP22657] Studies and Pooled Safety Population)

ae13_rel_gr34 Summary of Related Adverse Events NCI CTCAE Grade >= 3 With an Incidence >= 2%
Related Adverse Events
Protocol(s): PL00602 NP22657
Analysis: SAFETY Center: ALL CENTERS
Adverse Event Onset between Time of Very First Drug Intake and Study Day 9999, Time 23:59

Adverse Event	PLX06-02 N = 32 No. (%)	NP22657 N = 132 No. (%)	Pooled N = 164 No. (%)
SQUAMOUS CELL CARCINOMA OF SKIN	10 (31.3)	28 (21.2)	38 (23.2)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	2 (6.3)	12 (9.1)	14 (8.5)
RASH	1 (3.1)	9 (6.8)	10 (6.1)
ARTHRALGIA	1 (3.1)	8 (6.1)	9 (5.5)
BASAL CELL CARCINOMA	1 (3.1)	8 (6.1)	9 (5.5)
RASH MACULO-PAPULAR	-	8 (6.1)	8 (4.9)
ALANINE AMINOTRANSFERASE INCREASED	2 (6.3)	5 (3.8)	7 (4.3)
KERATOACANTHOMA	1 (3.1)	6 (4.5)	7 (4.3)
PHOTOSENSITIVITY REACTION	2 (6.3)	4 (3.0)	6 (3.7)
BLOOD ALKALINE PHOSPHATASE INCREASED	1 (3.1)	3 (2.3)	4 (2.4)
FATIGUE	2 (6.3)	2 (1.5)	4 (2.4)
ARTHRITIS	-	3 (2.3)	3 (1.8)
ASPARTATE AMINOTRANSFERASE INCREASED	2 (6.3)	1 (0.8)	3 (1.8)
BLOOD BILIRUBIN INCREASED	1 (3.1)	2 (1.5)	3 (1.8)
HYPOPHOSPHATAEMIA	1 (3.1)	2 (1.5)	3 (1.8)
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	1 (3.1)	2 (1.5)	3 (1.8)
PRURITUS	-	3 (2.3)	3 (1.8)
ANAEMIA	1 (3.1)	1 (0.8)	2 (1.2)
ASTHENIA	2 (6.3)	-	2 (1.2)
HYPERBILIRUBINAEMIA	1 (3.1)	1 (0.8)	2 (1.2)
HYPERTRIGLYCERIDAEMIA	2 (6.3)	-	2 (1.2)
HYPOKALAEMIA	1 (3.1)	1 (0.8)	2 (1.2)
NAUSEA	1 (3.1)	1 (0.8)	2 (1.2)
PROTEINURIA	2 (6.3)	-	2 (1.2)
RASH ERYTHEMATOUS	1 (3.1)	1 (0.8)	2 (1.2)
BLOOD AMYLASE INCREASED	1 (3.1)	-	1 (0.6)
DIARRHOEA	1 (3.1)	-	1 (0.6)
DYSAESTHESIA	1 (3.1)	-	1 (0.6)
HYPERGLYCAEMIA	1 (3.1)	-	1 (0.6)
IRIDOCYCLITIS	1 (3.1)	-	1 (0.6)
KERATOSIS PILARIS	1 (3.1)	-	1 (0.6)
LIPASE INCREASED	1 (3.1)	-	1 (0.6)
POLYARTHRITIS	1 (3.1)	-	1 (0.6)
RASH PAPULAR	1 (3.1)	-	1 (0.6)
SYNCOPE	1 (3.1)	-	1 (0.6)

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.

Supporting clinical pharmacology studies:

The majority (96%) of patients who received treatment with VEM in the three clinical pharmacology studies experienced at least one adverse event of any grade and the adverse event profile is comparable to that previously described in the Phase III and II studies. Again the level of severity and spectrum of adverse events documented were comparable to the previously described studies.

Deaths

Pivotal Phase III study NO25026:

In the pivotal Phase III study, there were more deaths in the dacarbazine group (23%) than in the VEM group (13%). The most common cause of death in both treatment groups was disease progression.

Studies PLX06-02 and NP22657:

A total of 53 patients (32%) in the pooled safety population died during the course of the two studies and 21 of these died within 28 days of their last dose of VEM treatment. With the exception of two deaths, one from pneumonia and one from acute renal failure, all deaths resulted from disease progression. The one death from renal failure was considered to be possibly related to VEM treatment. Further review considered that tumour lysis syndrome was predominant.

Supportive clinical pharmacology studies:

Seven (8%) of patients in the three clinical pharmacology studies died from disease progression and there were no other causes of death.

Other serious adverse events:

In the Phase III NO25026 study a higher percentage of VEM patients (33%) than dacarbazine patients (16%) experienced serious adverse events (SAEs). The most common treatment related SAEs in the VEM group were cutaneous SCC in 11% and keratoacanthoma in 7% of patients. All of these symptoms were considered to be treatment related by the study investigator. Dacarbazine related SAEs were mostly haematologic in nature.

A higher percentage of patients (52%) in the pooled safety population of the Phase I and Phase II studies and a lower percentage of patients (26%) across the three clinical pharmacology studies reported SAEs, however the types of events reported were similar to those observed in the Phase III study.

One VEM treated patient in the Phase III study developed Stevens-Johnson syndrome and one patient in the clinical pharmacology Study NP25163 experienced shock that was characterised as a hypersensitivity reaction and included a constellation of symptoms including hypertension, flushing and pyrexia.

Adverse events leading to premature withdrawal:

Pivotal Phase III study NO25026

As of the clinical cut off-date for the Phase III study, adverse events leading to treatment withdrawal occurred in 19 patients (6%) of the VEM group and 12 patients (4%) in the dacarbazine group as summarised in Table 28. Specific adverse events leading to withdrawal occurred in two or fewer patients each.

Table 28. Summary of AEs leading to treatment discontinuation by intensity (Phase III NO25026 Study, Safety population). Table continued across four pages.

/ vent	Total No.	Total (%)	CTC Grading 1 No.	1 (%)	2 No.	2 (%)	3 No.	3 (%)	4 No.	4 (%)	5 No.	5 (%)
Treatment: DTIC; N = 282												
ALL BODY SYSTEMS												
Total Pts with at Least one AE	12	(4)	-		2	(<1)	7	(2)	2	(<1)	3	(1)
Total Number of AEs	19		-		2		8		3		6	
GASTROINTESTINAL DISORDERS												
Total Pts With at Least one AE	4	(1)	-		2	(<1)	2	(<1)	1	(<1)	-	
VOMITING	2	(<1)	-		1	(<1)	1	(<1)	-		-	
ABDOMINAL PAIN LOWER	1	(<1)	-		-		-		1	(<1)	-	
GASTROINTESTINAL HAEMORRHAGE	1	(<1)	-		-		1	(<1)	-		-	
NAUSEA	1	(<1)	-		1	(<1)	-		-		-	
Total Number of AEs	5		-		2		2		1		-	
VASCULAR DISORDERS												
Total Pts With at Least one AE	3	(1)	-		-		1	(<1)	1	(<1)	1	(<1)
HYPOTENSION	1	(<1)	-		-		1	(<1)	-		-	
SHOCK	1	(<1)	-		-		-		-		1	(<1)
THROMBOSIS	1	(<1)	-		-		-		1	(<1)	-	
Total Number of AEs	3		-		-		1		1		1	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS												
Total Pts With at Least one AE	2	(<1)	-		-		1	(<1)	1	(<1)	-	
DYSPNOEA	1	(<1)	-		-		1	(<1)	-		-	
PLEURAL EFFUSION	1	(<1)	-		-		1	(<1)	-		-	
PULMONARY EMBOLISM	1	(<1)	-		-		-		1	(<1)	-	
Total Number of AEs	3		-		-		2		1		-	
NERVOUS SYSTEM DISORDERS												
Total Pts With at Least one AE	2	(<1)	-		-		1	(<1)	-		1	(<1)
CEREBROVASCULAR ACCIDENT	1	(<1)	-		-		1	(<1)	-		-	
MYELITIS TRANSVERSE	1	(<1)	-		-		-		-		1	(<1)
Total Number of AEs	2		-		-		1		-		1	
BLOOD AND LYMPHATIC SYSTEM DISORDERS												
Total Pts With at Least one AE	1	(<1)	-		-		1	(<1)	-		1	(<1)
FEBRILE NEUTROPENIA	1	(<1)	-		-		1	(<1)	-		-	
LEUKOPENIA	1	(<1)	-		-		-		-		1	(<1)
NEUTROPENIA	1	(<1)	-		-		-		-		1	(<1)
THROMBOCYTOPENIA	1	(<1)	-		-		-		-		1	(<1)
Total Number of AEs	4		-		-		1		-		3	
CARDIAC DISORDERS												
Total Pts With at Least one AE	1	(<1)	-		-		-		-		1	(<1)
CARDIOPULMONARY FAILURE	1	(<1)	-		-		-		-		1	(<1)
Total Number of AEs	1		-		-		-		-		1	

Table 28 continued.

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Treatment: DTIC; N = 282 (continued)						
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)						
Total Pts With at Least one AE	1 (<1)	-	-	1 (<1)	-	-
METASTASES TO CENTRAL NERVOUS SYSTEM	1 (<1)	-	-	1 (<1)	-	-
Total Number of AEs	1	-	-	1	-	-
Treatment: RO5185426; N = 336						
ALL BODY SYSTEMS						
Total Pts with at Least one AE	19 (6)	3 (<1)	6 (2)	13 (4)	-	3 (<1)
Total Number of AEs	26	3	7	13	-	3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Total Pts With at Least one AE	3 (<1)	1 (<1)	2 (<1)	-	-	-
FATIGUE	1 (<1)	-	1 (<1)	-	-	-
GAIT DISTURBANCE	1 (<1)	1 (<1)	-	-	-	-
PAIN	1 (<1)	-	1 (<1)	-	-	-
Total Number of AEs	3	1	2	-	-	-
INVESTIGATIONS						
Total Pts With at Least one AE	3 (<1)	-	-	3 (<1)	-	-
BLOOD ALKALINE PHOSPHATASE INCREASED	1 (<1)	-	-	1 (<1)	-	-
BLOOD BILIRUBIN INCREASED	1 (<1)	-	-	1 (<1)	-	-
GAMMA-GLUTAMYLTRANSFERASE INCREASED	1 (<1)	-	-	1 (<1)	-	-
Total Number of AEs	3	-	-	3	-	-
GASTROINTESTINAL DISORDERS						
Total Pts With at Least one AE	2 (<1)	1 (<1)	2 (<1)	1 (<1)	-	-
DYSPHAGIA	2 (<1)	-	2 (<1)	-	-	-
DYSPEPSIA	1 (<1)	-	-	1 (<1)	-	-
GASTROOESOPHAGEAL REFLUX DISEASE	1 (<1)	1 (<1)	-	-	-	-
Total Number of AEs	4	1	2	1	-	-
EYE DISORDERS						
Total Pts With at Least one AE	2 (<1)	-	2 (<1)	-	-	-
CONJUNCTIVAL HYPERAEMIA	1 (<1)	-	1 (<1)	-	-	-
DIPLOPIA	1 (<1)	-	1 (<1)	-	-	-
Total Number of AEs	2	-	2	-	-	-

Table 28 continued.

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Treatment: RO5185426; N = 336 (continued)						
INFECTIONS AND INFESTATIONS						
Total Pts With at Least one AE	2 (<1)	-	-	1 (<1)	-	1 (<1)
PNEUMONIA	2 (<1)	-	-	1 (<1)	-	1 (<1)
Total Number of AEs	2	-	-	1	-	1
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)						
Total Pts With at Least one AE	2 (<1)	-	-	-	-	2 (<1)
INTRACRANIAL TUMOUR HAEMORRHAGE	1 (<1)	-	-	-	-	1 (<1)
METASTASES TO CENTRAL NERVOUS SYSTEM	1 (<1)	-	-	-	-	1 (<1)
Total Number of AEs	2	-	-	-	-	2
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Total Pts With at Least one AE	2 (<1)	-	-	2 (<1)	-	-
STEVENS-JOHNSON SYNDROME	1 (<1)	-	-	1 (<1)	-	-
TOXIC SKIN ERUPTION	1 (<1)	-	-	1 (<1)	-	-
Total Number of AEs	2	-	-	2	-	-
BLOOD AND LYMPHATIC SYSTEM DISORDERS						
Total Pts With at Least one AE	1 (<1)	-	-	1 (<1)	-	-
THROMBOCYTOPENIA	1 (<1)	-	-	1 (<1)	-	-
Total Number of AEs	1	-	-	1	-	-
CARDIAC DISORDERS						
Total Pts With at Least one AE	1 (<1)	-	-	1 (<1)	-	-
ATRIAL FIBRILLATION	1 (<1)	-	-	1 (<1)	-	-
Total Number of AEs	1	-	-	1	-	-
HEPATOBILIARY DISORDERS						
Total Pts With at Least one AE	1 (<1)	-	-	1 (<1)	-	-
HEPATITIS ACUTE	1 (<1)	-	-	1 (<1)	-	-
Total Number of AEs	1	-	-	1	-	-
METABOLISM AND NUTRITION DISORDERS						
Total Pts With at Least one AE	1 (<1)	-	1 (<1)	-	-	-
DEHYDRATION	1 (<1)	-	1 (<1)	-	-	-
Total Number of AEs	1	-	1	-	-	-

Table 28 continued.

Body System/ Adverse Event	Total No.	Total (%)	CTC Grading 1 No.	1 (%)	2 No.	2 (%)	3 No.	3 (%)	4 No.	4 (%)	5 No.	5 (%)
Treatment: RO5185426; N = 336 (continued)												
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS												
Total Pts With at Least one AE	1	(<1)	1	(<1)	-		-		-		-	
ARTHRALGIA	1	(<1)	1	(<1)	-		-		-		-	
Total Number of AEs	1		1		-		-		-		-	
NERVOUS SYSTEM DISORDERS												
Total Pts With at Least one AE	1	(<1)	-		-		1	(<1)	-		-	
COGNITIVE DISORDER	1	(<1)	-		-		1	(<1)	-		-	
Total Number of AEs	1		-		-		1		-		-	
RENAL AND URINARY DISORDERS												
Total Pts With at Least one AE	1	(<1)	-		-		1	(<1)	-		-	
RENAL IMPAIRMENT	1	(<1)	-		-		1	(<1)	-		-	
Total Number of AEs	1		-		-		1		-		-	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS												
Total Pts With at Least one AE	1	(<1)	-		-		1	(<1)	-		-	
CHOKING	1	(<1)	-		-		1	(<1)	-		-	
Total Number of AEs	1		-		-		1		-		-	

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
*** Missing preferred terms are replaced by investigator text.
AE17 03MAR2011:03:02:31

Studies PLX06-02 and NP22657

Four patients (2%) in the pooled safety population experienced adverse events that led to premature withdrawal from treatment including delirium, increased liver function, retinal vein occlusion and cellulitis.

Supporting clinical pharmacology studies

Of the 84 patients enrolled in the three clinical pharmacology studies, two patients prematurely withdrew from treatment due to adverse events including pyrexia and one patient with a hypersensitivity reaction.

Adverse events leading to death, modification or interruption

In the Phase III NO25026 study more VEM treated patients (38%) than dacarbazine treated patients (16%) modified their dose due to an adverse event. VEM dose modifications were mostly because of skin rash (primarily Grade III), elevated liver function tests (primarily Grade II and III), arthralgia and pyrexia. Dacarbazine dose modifications were mostly haematologic in nature.

A higher percentage of patients (57%) in the pooled safety population and a lower percentage of patients (30%) across the three clinical pharmacology studies modified their doses due to an adverse event, however the types of adverse events that lead to dose modification were similar to those observed in the Phase III study.

Adverse events of special interest

These events were chosen because of a safety signal emanating from nonclinical and clinical studies or their presence as dose limiting toxicities and included rash, cutaneous SCC, photosensitivity, fatigue, arthralgia, liver laboratory abnormalities and QT prolongation. Overall the majority of patients treated with VEM in the Phase III study, that is 302 patients were 90% and 98% in the pooled safety population, experienced at least one adverse event of special interest (AESI) during the study. The most frequently reported were rash, arthralgia, fatigue and photosensitivity. The most frequently reported events of at least Grade III severity was cutaneous SCC with some patients experiencing multiple lesions. The following text reviews the individual adverse events of special interest.

Squamous cell carcinoma

Approximately 20% of all VEM treated patients developed cutaneous SCC across all studies. Among patients who developed the cutaneous SCC, the mean time to onset ranged from 8.3–8.6 weeks and the median ranged from 7.1–8.1 weeks. Among patients who developed more than one lesion (29 – 38%) the mean/median time to second recurrence was approximately six weeks. Patients who developed cutaneous SCC tended to be on oral VEM longer than average and hence received more study medication than those who did not develop cutaneous SCC. However, the average daily dose received was approximately the same across both groups. Central dermatopathology evaluation showed that the majority of cutaneous SCC lesion biopsies were of keratoacanthoma (KA) or mixed KA sub-type. There were no incidences of non cutaneous SCC. Across all studies the association of age with the development of treatment emergent cutaneus SCC was significant, with patients aged at least 65 years had approximately 2.5 to 5 times greater chance of developing cutaneous SCC compared to younger patients. In the Phase III study the risk of treatment emergent cutaneous SCC was more than double for patients who reported a history of chronic sun exposure compared to those that did not. In the pooled studies a prior history of skin cancer was also figured in the risk factors. The effect of gender was not statistically significant in any of the studies.

Rash

Rash was the most common AESI reported by 60% of VEM patients in the Phase III study, 72% in the pooled safety population and 64% of patients across the three clinical pharmacology studies. Among patients who developed rash adverse events, the mean/median time to first onset was approximately 2 to 4 weeks. Approximately 12-15% of patients in the Phase III study and pooled safety population experienced at least a Grade III rash. There were no Grade IV or Grade V rashes. Approximately 20% of patients had rash leading to dose modification of study treatment. No patients required treatment discontinuation because of rash.

Photosensitivity

Photosensitivity adverse events were experienced by 37% of VEM patients in the Phase III study, 61% of the patients in the pooled safety population and 37% of patients across the three clinical pharmacology studies. Among those patients who developed photosensitivity adverse events the mean/median time to first onset was approximately 2 to 6 weeks. Photosensitivity adverse events of Grade III were uncommon being experienced in 3-4% of patients across all studies and there were no Grade IV or V events reported. Approximately 2 to 5% of patients had the dose modification study treatment but no patients discontinued VEM because of photosensitivity.

Arthralgia

Arthralgia events were experienced by 49% of VEM patients in the Phase III study, 69% of patients in the pooled safety population and 46% across the three clinical pharmacology studies. Among those patients who developed events of arthralgia the mean time to first onset was approximately 4 to 6 weeks and median was approximately two weeks. Events of Grade III arthralgia were not common appearing in 3-7% of patients across the studies without any Grade IV or V events being reported. Some 11 to 13% of events led to dose modification study and one patient in the Phase III study discontinued VEM treatment because of arthralgia which resolved after discontinuation.

Fatigue

Fatigue adverse events were experienced by 41% of VEM patients in the Phase III study, 62% of patients in the pooled safety population and 52% of patients across the three clinical pharmacology studies. Among those patients who developed fatigue adverse events, the mean time to onset was 5 to 9 weeks and the median was 3 to 6 weeks. Grade III fatigue adverse events were uncommon occurring in 2 to 4% of patients. Approximately 11 to 13% of events led to dose modification of study treatment and one patient experienced a Grade IV event of asthenia. Two patients discontinued VEM treatment due to fatigue and AESI events.

Liver laboratory abnormalities

Liver function abnormalities developed in 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 abnormalities, the mean time to first onset was 6 to 7 weeks and the median was 3 to 6 weeks. Grade III liver function abnormalities occurred in 7 to 12% of patients and Grade IV events were recorded in 1 to 4% of patients. There was no Grade V liver function abnormalities reported. A total of 28 to 40% of events led to dose modification of study treatment. Four patients discontinued VEM treatment due to liver laboratory abnormalities, all of which improved after treatment discontinuation. Overall liver laboratory abnormalities were generally reversible with dose modification or discontinuation.

QT prolongation

Adverse events potentially associated with prolongation of cardiac repolarisation or arrhythmia were reported in 8% of patients in the Phase III study, 9% of patients in the pooled safety population and 6% of patients across the three clinical pharmacology studies, the most common of which was dizziness. Among those patients who developed QT prolongation adverse events the mean time to first onset was 6 to 8 weeks and the median was three weeks. Grade III QT prolongation adverse events were uncommon being <1% across studies, although three QT prolongation adverse events were serious in the Phase III study including two events of loss of consciousness and one of syncope. These symptoms resolved on treatment interruption and then treatment was able to be resumed. No patients discontinued treatment due to QT prolongation adverse event and only one patient required dose modification.

Rare but clinically meaningful adverse events

Several rare but clinically meaningful adverse events were reported and included four events of facial nerve paralysis (one in the Phase III study and three in the Phase II Study NP22657), 11 events of uveitis (four in the Phase III study, five in the Phase II study and two in the Phase I study PLX06-02) and one event of retinal vein occlusion in the Phase II study. The adverse events of facial palsy and uveitis were mild or moderate in intensity and did not lead to discontinuation of study drug. The majority resolved without drug interruption. The single event of retinal vein occlusion in Study NP22657 was severe and serious in nature and led to discontinuation of study drug. The event improved but did not resolve following cessation of therapy.

Clinical laboratory evaluations

Across all studies post baseline shifts and change in laboratory parameters to Grade III or IV were uncommon and were noted in <5% of patients. Phase III study laboratory parameters where post baseline shifts to Grade III or IV occurred in at least 5% of patients including decreased neutrophils, white blood count, lymphocytes and increased GGT. The overall incidence of worsening liver function tests, one grade increased from baseline was higher in the VEM group than the dacarbazine group. Worsening GGT, ALP and ALT levels occurred at a similar incidence in both treatment groups while worsening of AST, ALP and bilirubin occurred at a higher incidence in the VEM group than in the dacarbazine group. In the pooled safety population the most commonly reported Grade III or greater laboratory abnormality was elevated GGT.

Liver function tests

The overall incidence of worsening liver function tests, that is, one grade increase from baseline was higher in the VEM group (238 patients or 74%) than in the dacarbazine group (133 patients or 50%). Worsening of GGT levels occurred in 34% of patients given VEM and 38% of patients given Dacarbazine, while increased ALT occurred in 35% of patients given VEM and 31% of patients given dacarbazine. This was a comparable incidence for both treatment groups. There was a higher incidence of worsening AST (32% of patients in the VEM group and 18% of the dacarbazine group), ALP (38% for VEM and 14% for dacarbazine) and bilirubin levels (34% for VEM and 7% for dacarbazine) in VEM patients. For patients who had an event, the median time to first onset of GGT, AST and ALT levels worsening was longer in the VEM group than the dacarbazine group (GGT: 3.1 weeks for VEM versus 1.2 weeks for dacarbazine; AST: 3 weeks for VEM versus 1.1 week for dacarbazine; ALT: 3 weeks for VEM versus 1 week for dacarbazine) but comparable between groups for ALP (3 weeks for VEM versus 2.7 weeks for dacarbazine) and bilirubin (3 weeks in both groups). Fewer than 5% of patients in either treatment group had Grade III or IV grade change from baseline liver function test. Upon clinical review no patient had

concurrent ALT/AST elevation to >3 times upper limit of normal and total bilirubin increases to >2 times upper limit of normal without ALP elevation.

Vital signs

Across all studies no clinically meaningful changes in either systolic blood pressure or diastolic blood pressure were observed among the VEM treated patients.

Electrocardiograms

In the Phase III studies the mean change from baseline in QT, QTc, QTcB and QTcF intervals was greater in the VEM group than the dacarbazine group at all times after dosing. A similar proportion of patients in the VEM and dacarbazine groups exhibited a treatment emergent maximum individual QTcB and QTcF change from baseline of >60 ms and no maximum individual QTcF values of >500 ms was seen in either treatment group.

In the pooled safety population, two patients developed treatment emergent absolute QTcP values of >500 ms and one of these patients also had a QTcP change from baseline of >60 ms. It is noteworthy that most events potentially associated with pro arrhythmic events were not associated with concomitant QTcF >450 ms.

Adverse events involving dizziness and loss of consciousness have been discussed previously in this AusPAR. It is noteworthy that two patients developed adverse events relating to other cardiac function disorders; cardiomegaly in one patient and left atrial dilatation in another. None of these were serious with the left atrial dilatation resolving without sequelae although the cardiomegaly was ongoing.

In the Phase II Study NP22657 relevant adverse events other than dizziness and loss of consciousness included one patient developing left ventricular hypertrophy of a Grade I level and two cases of sinus tachycardia of a Grade I level considered related to treatment.

Safety in special groups

Age

In the pivotal Phase III study approximately 25% of patients were aged 65 years or older. A review of adverse events revealed that in these patients there was a higher incidence of adverse events, in particular nausea, actinic keratoses, peripheral oedema, skin SCC, KA, decreased appetite, depression and atrial fibrillation. With respect to serious adverse events of at least Grade III severity, patients 65 years or older experienced a higher incidence of SCC of the skin (19% versus 8% for young patients), rash (13% versus 7%) and GTT (4% versus 2%) than the younger patients. Certain adverse events however occurred more frequently in younger patients and those of at least Grade IV intensity affecting patients <65 years to a greater degree included photosensitivity (4% versus 0%) and maculopapular rash (3% versus 1%). It is noteworthy that laboratory data were comparable between the various age groups of patients. Data from the Phase I and Phase II studies in relation to age also reflected these differences.

Gender

When all adverse events regardless of age are graded or examined, the overall profiles suggested a trend for increased reporting of adverse events in female patients versus male patients in the VEM group. However certain adverse events were higher in males than females and included pruritus, dysgeusia, KA and folliculitis. When adverse events of at least Grade III level were examined, three occurred at a higher incidence in females than males when on VEM therapy; rash (12% females versus 6% males), arthralgia (5% females versus 2% males) and photosensitivity reaction (4% females versus 2% males). Overall laboratory data were comparable between male and female patients in the VEM group with the exception of Grade III increased ALP (4% versus 2% in females) and

increased total bilirubin in males (3% versus 1% females) while the incidence of increased creatinine levels was higher in females (3% versus 1%).

ECG by age and gender

A review of the Phase III study revealed that among male patients the incidence of ECG findings in patients treated with VEM was higher than or comparable to that in patients treated with dacarbazine except for QTcB values of >500 ms which was proportionally higher in the male patients treated with dacarbazine. Among female patients the incidence of ECG findings in patients treated with VEM was higher than or comparable to that in patients treated with dacarbazine with the exception of a maximum individual change in QTc interval >60 ms which was higher in female patients treated with dacarbazine.

In relation to age, the percentage of patients with QTcB, QTcB and QTcF values >450 ms or 480 ms was greater in the older sub group than in the younger subgroup. The percentage of dacarbazine but not VEM patients who reported QTcB values >500 ms was higher in the older sub group (4.3%) than the younger group (0.6%). The percentage of patients with maximum individual QTc changes >60 ms was higher among patients <65 years of age (67.4%) than in the older patients (4.7%) for those treated with VEM.

Post marketing data

VEM is not presently commercially available in any part of the world and therefore there is no post marketing data.

Evaluator comment

Safety profile demonstrated from pivotal Study NO25026 as well as the five supporting studies indicates a relatively predictable safety profile. Treatment related adverse events generally occur fairly early within 1-2 months of initiation of treatment. The vast majority of adverse events were mild to moderate in nature, although dose modifications were required in approximately 40% of patients who received the standard dose of 960 mg twice daily, which generally could be managed by relatively short interruption or dose reduction. The overall most common adverse events described included arthralgia, rash, alopecia, fatigue, nausea and photosensitivity. Again these were predominantly mild to moderate in intensity. It was noted that in the Phase III study a higher proportion of patients developed Grade III adverse events whilst receiving VEM compared to dacarbazine, although the proportion of patients demonstrating Grade IV events were higher in the dacarbazine group. Adverse events leading to treatment withdrawal were uncommon and there were only two deaths within all studies considered directly attributable to VEM. Of particular interest was the rather high incidence of cutaneous SCCs as well as liver function test abnormalities. The former requires appropriate monitoring and action on development. The latter certainly requires relevant monitoring although clinical sequelae were fairly uncommon in relation to the hepatic function test abnormalities. The other area requiring careful monitoring includes appropriate regular ECGs as changes in QT intervals were fairly common among patients receiving VEM although again clinical sequelae were relatively uncommon.

Overall it is considered that the safety profile for VEM is generally manageable with appropriate monitoring and early intervention. There is no evidence available from the study submitted of a higher incidence of severe or irreversible adverse effects.

Clinical summary and conclusions

First round assessment of benefits

VEM represents a first in class selective inhibitor of mutated BRAF kinase. Studies undertaken in patients with metastatic or unresectable melanoma who have $BRAF^{V600}$

mutations (tumour samples tested mutation positive by the cobas BRAF 4800 BRAF V600 Mutation Test) including the Phase III randomised pivotal Study NO25026 in which patients were randomly assigned to receive either VEM at 960 mg twice daily as an oral medication or control therapy dacarbazine, a Phase II Study NP22657, the Phase I Study PLX06-02 and the three clinical pharmacology studies have clearly shown evidence of major therapeutic benefits. The randomised study has shown a highly significant as well clinically important improvement in primary outcomes including overall survival and progression free survival when compared to dacarbazine. Furthermore, the overall response rate was higher than has been seen with any other single agent utilised in the management of metastatic melanoma. The response rate of the order of 50% is more than three times greater than that previously observed with other therapies including dacarbazine. The randomised study was quite large and robust involving a total of 675 patients, while the Phase II study involved 132 patients again reinforcing the therapeutic benefit of VEM in these patients. It is also noteworthy that apart from key efficacy endpoints, VEM treatment was associated with improved outcomes across all sub groups for stratification factors and among patients with more rare V600 mutations other than V600E.

First round assessment of risks

The safety data base included in the application provides safety information on 584 patients receiving VEM who received at least one dose of study drug. The overall safety profile was characterised predominantly by commonly occurring adverse events of rash, alopecia, photosensitivity, arthralgia and gastrointestinal disorders. The majority of these adverse events were Grade I to II in intensity and readily reversible on short term treatment discontinuation or modification of dose. More significant were adverse events including the development of cutaneous SCC and liver function abnormalities as well as the occasional severe hypersensitivity reaction all of which require careful monitoring and early intervention. A small proportion of patients, that is <6%, required discontinuation of treatment and only two deaths considered directly attributable to VEM therapy occurred across the clinical studies presented.[24] Accordingly, the evidence would support an overall adverse event profile which was considered generally tolerable and can be effectively managed with appropriate monitoring and early intervention.

First round assessment of benefit/risk balance

As indicated above the evidence of therapeutic benefit for VEM in patients with metastatic or unresectable melanoma who are V600 mutation positive is convincing and well beyond that previously observed for available therapies for these patients. The risk profile is generally manageable with a relatively low incidence of severe and unpredictable adverse effects. Accordingly this evaluator considered that the risk/benefit profile clearly favours the benefits of VEM in this population of patients.

First round recommendation regarding authorisation

This evaluator on the balance of the very positive results from the clinical trials together with the manageable safety profile recommends approval for the marketing of vemurafenib for the treatment of unresectable Stage IIIC or Stage IV metastatic melanoma positive for $BRAF^{V600}$ mutation.

[24] Sponsor comment: "A small proportion of patients, that is, <6% required discontinuation of treatment and only one death considered possibly attributable to VEM therapy occurred across the clinical studies presented."

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing safety Concerns which are summarised below.

Important identified risks:

- Cutaneous Squamous Cell Carcinoma (SCC)
- Liver Laboratory Abnormalities
- Photosensitivity/Sunburn
- Arthralgia
- Rash
- Fatigue
- QTc Prolongation

Important potential risks:

- Non-cutaneous Squamous Cell Carcinoma
- VIIth Nerve paralysis
- Hypersensitivity
- Retinal Vein Occlusion
- Uveitis

OPR reviewer comment

The above summary of the Ongoing Safety Concerns was considered acceptable.

Pharmacovigilance plan

The sponsor states that routine pharmacovigilance activities that fulfil the requirements of Volume 9A of "The Rules Governing Medicinal Products in the European Union" and "The Guidelines on Monitoring of Compliance with Pharmacovigilance Regulatory Obligations and Pharmacogivilance Inspections for Centrally Authorised Products" will be conducted and include all safety concerns.

For the identified risk of cutaneous squamous cell carcinoma and potential risk of non-cutaneous squamous cell carcinoma, Roche will continue to submit reports which summarize SCC events in vemurafenib clinical trials. This will be semi-annually post registration concurrent with periodic safety update reports (PSURs).

Additionally, for the identified risk of cutaneous squamous cell carcinoma, it is proposed that:

- an epidemiological study titled "Cutaneous Squamous Cell Carcinoma Risk in a Cohort of Kaiser Permanente Northern California Members with Cutaneous Melanoma" will be conducted:
    - Primary objective: to examine the incidence of cutaneous SCC among a cohort of Kaiser Permanente of Northern California (KPNC) members diagnosed with melanoma from 1 January 2000 to 31 December 2005.

- Secondary objective to examine how co-variates (such as age, gender, ethnicity, tumour characteristics, tumour treatment) impact the outcome of SCC
- Study population: adults and children, diagnosed with cutaneous melanoma, health plan members diagnosed with cutaneous melanoma as reported to the Northern California Cancer Registry for the period defined above
- Outcome: subsequent SCC
- Sample size: approximately 1000-1200 incident of cutaneous melanoma cases (15-20 cases/100,000 members) have been recorded per year in the registry.
- Planned end date: December 2011, with data available third quarter 2012.

- A nonclinical study to further investigate the mechanism of action on development of cutaneous SCC related to VEM treatment:
  - To explore the role of mutated *HRAS* in contributing to development of cutaneous SCC.
  - Rationale: a substantial portion of cutaneous SCC lesions from patients treated with VEM in clinical trials have *HRAS* mutations, which might suggest that existing *HRAS* mutations could predispose to development of cutaneous SCC instead of de novo development caused by VEM treatment.
  - No protocol will be established as it is a nonclinical exploratory study and results will be reported to Health Authorities.
  - Anticipated data to be available by end of 2011.

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

The use of routine pharmacovigilance, supplemented by the epidemiological study on cutaneous SCC was considered appropriate given the target population for this medication and the prescribing population.

Risk minimisation activities

The sponsor states that the risks are adequately described in the prescribing information, and this is adequate to manage the risks. No additional risk minimisation activities are planned.

OPR reviewer comment

The use of routine activities (PI and CMI) is considered appropriate given the nature of the condition, target of population and prescribing group.

In regard to the proposed routine risk minimisation activities, the draft PI and CMI are generally acceptable. However, it is stated in the current submission that "*no package insert will be provided with this product*". It is unclear if the package insert refers to the Consumer Medicine Information and if so, the sponsor will need to assure that the relevant information about the use of the product and associated risks will be appropriately communicated to the consumers as part of the routine risk minimisation strategy.

It is noted that there are some discrepancies between some information that is presented in the approved US FDA product label (version 8/2011) and those presented in the proposed Australian PI. Notable safety information and/or adverse reactions that are included in the US FDA product label but had not been included (or are different) in the proposed Australian PI were detailed by the evaluator.

Summary of recommendations

In the event that this application is successful, the OPR recommends the implementation of Vemurafenib Risk Management Plan version 1.0, dated May 2011 (both EU and Australian), and any future updates, be included as a condition of registration.

If this submission was to be approved, it was also recommended that the Delegate considers if the sponsor can provide assurance that the proposed routine risk minimisation activity will be implemented in Australia such as the supply of Consumer Medicine Information with the product, to ensure that the relevant information on the use of the product and associated risks is appropriately conveyed to the consumers, as it is stated in the current submission that "*no package insert will be provided with this product*.

Discrepancies in the information presented in the approved US FDA product label (revision 8/2011) and those presented in the proposed Australian PI were noted and highlighted to the Delegate.

VI. Overall conclusion and risk/benefit assessment

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

Quality

- Vemurafenib is a synthetic substance with unstable crystalline forms and more stable but less soluble non-crystalline forms. An optimised MBP formulation is proposed for registration. The lack of an absolute bioavailability study was not adequately justified. Absolute bioavailability is likely to be low and variable because of the drug's low solubility.
- A study of the effect of food on vemurafenib pharmacokinetics (NP25396) is ongoing. The study report is anticipated in the second quarter of 2012. At present, it is recommended that vemurafenib be taken on an empty stomach (one h before or 2 h after food).
- The sponsor has been asked to tighten the limit for unspecified impurities in the drug substance. If not tightened or suitably justified, a tighter limit will be considered as a condition of registration.
- The application was reviewed at the 142nd meeting of the Pharmaceutical Subcommittee (PSC) on 21 November 2011.

The quality evaluator supported registration.

Nonclinical

- Vemurafenib inhibited BRAF V600 mutant kinase activity reducing MAPK/ERK and MEK signalling and inhibiting proliferation of melanoma cells in a mouse model with a human melanoma xenograft. There was also significant inhibition of 18 other kinases. Resistance developed relatively quickly.
- The full toxicological profile of vemurafenib is unlikely to have been revealed because of subclinical animal exposure. Toxicological findings included potentiation of cutaneous squamous cell carcinoma (SCC), QT prolongation in the electrocardiogram, hepatotoxicity, gastrointestinal disturbance and phototoxicity.

There was insufficient information for the nonclinical evaluator to assess the benefit-risk profile of vemurafenib.

Clinical

Pharmacology

- The maximum tolerated dose of the MBP formulation of vemurafenib was 960 mg bd (Study PLX06-02; *Clinical Evaluation* (CE) summarised under *Clinical Findings* in this AusPAR). This was the dose used in the efficacy studies. Dose limiting toxicities were Grade 3 rash and fatigue.
- The pharmacokinetic Study NP25163 showed linear pharmacokinetics over the dose range 240 to 960 mg bd. In the 960 mg bd cohort (n=16), the median time to maximum vemurafenib plasma concentration was 5 h, range 2-8 h on the first day of dosing. Steady-state plasma concentrations were reached after about 15 days.
- With 920 mg bd oral dosing, there was marked accumulation of vemurafenib over the dose interval. In a population pharmacokinetic analysis of three studies (the pharmacokinetic study NP25163, a Phase II efficacy Study NP22657 and a Phase III efficacy Sstudy NO25026) in 458 metastatic melanoma patients, the median accumulation factor was 6.7. There was considerable variability between patients. Food intake was not controlled. The estimated volume of distribution of vemurafenib was 91 L and the plasma clearance 29 L/day. Median plasma elimination half life was 57 h.
- In a mass balance study in six metastatic melanoma patients (NP25158), vemurafenib was eliminated primarily by the liver and excreted in faeces mostly as unchanged drug. Less than 1% was excreted in urine.
- Vemurafenib exposure is likely to be increased in patients with hepatic impairment. There was no study in these patients. The USA has required a study as a post market commitment.
- The effect of vemurafenib on five CYP450 substrates was assessed in Study NP22676 in metastatic melanoma patients (n=20). Vemurafenib significantly increased caffeine exposure (CYP1A2 substrate) and significantly reduced midazolam exposure (CYP3A4 substrate). Hence, vemurafenib inhibits CYP1A2 and induces CYP3A4. Whilst there was no significant impact on warfarin exposure, caution is recommended when vemurafenib is administered with warfarin since warfarin exposure increased in some patients .
- In a sub-study of the Phase II efficacy Study NP22657 (n=132), vemurafenib 960 mg bd prolonged the ECG QTc interval by a mean 12-15 ms. QTc exceeded 500 ms in two patients (1.5%) and QTc change exceeded 60 ms in one patient (0.8%).

Efficacy

- The efficacy of vemurafenib in BRAF V600E mutation-positive advanced melanoma was assessed in three trials, a controlled trial in first line patients (NO25026), an uncontrolled trial in second line patients (NP22657) and an uncontrolled trial in first and second line patients PLX06-02 (melanoma extension cohort). The mutation was detected using the cobas 4800 BRAF V600 Mutation Test in trials NO25026 and NP22657 and an early prototype test in Study PLX06-02. The test was designed to detect the V600E mutation with high sensitivity. The test was also positive in the presence of some other V600 mutations; however, the validity of the test for detecting other V600 mutations was not assessed (sponsor's *Clinical Overview*).
- Study NO25026 was a randomised, open label trial in previously untreated patients with BRAF V600E mutation-positive unresectable Stage IIIC or Stage IV melanoma. The trial was multinational including Australia. Patients received either vemurafenib (Zelboraf) tablets 960 mg bd (n=337) or dacarbazine IV 1,000 mg/m^2 every 3 weeks (n=338). The comparator is a recognised standard treatment (*Cancer*

Institute NSW). The median age of vemurafenib subjects was 56 years (range 21-86) and dacarbazine subjects 53 years (range 17-86). ECOG performance status was 0 or 1. Treatment was continued until disease progression. The median (range) follow-up was 3.8 months (0.3-10.8) with vemurafenib and 2.3 months (0.1-10.3) with dacarbazine. There were two primary endpoints, overall survival and progression-free survival.

- Vemurafenib significantly increased overall survival and progression-free survival compared with dacarbazine (Table 29). Best overall response rate was also significantly better with vemurafenib.

Table 29. Efficacy in previously untreated unresectable BRAF V600E mutation-positive stage IIIC or IV melanoma (Study NO25026) – *intent-to-treat*

	Vemurafenib 960 mg bd po n=337	Dacarbazine 1,000 mg/m² q3w *iv* *n=338*	Hazard Ratio [95% CI] or p-value of diff
Survival 6-mth *%*	84%	64%	0.37
median *mths*	9.2[2]	7.8[2]	[0.26, 0.55]
PFS[1] 6-mth *%*	47%	12%	0.26
median *mths*	5.3	1.6	[0.20, 0.33]
BORR[1]	48.4% (n=219)	5.5% (n=220)	p<0.0001
Complete Response	0.9%	0	
Partial Response	47.5%	5.5%	
Duration of Response			
median *mths*	5.5	NR[3]	

[1] Investigator assessed (RECIST 1.1 criteria). [2] Not reliable due to short follow-up: < 10% of patients followed up beyond month 7. [3] Not reliable due to few responders. PFS: progression-free survival. BORR: confirmed best overall response rate (complete response + partial response). NR: not reached. 6-mth and median survival, PFS and response duration estimated using Kaplan-Meier analysis. Hazard ratios estimated using Cox models.

- Study NP22657 was an uncontrolled trial in previously treated patients with BRAF V600E mutation-positive stage IV melanoma. Patients received vemurafenib (Zelboraf) tablets 960 mg bd (n=132). The median age of subjects was 52 years (range 17-82). ECOG performance status was 0 or 1. Treatment was continued until disease progression. The median (range) follow-up was 6.9 months (0.6-11.3). Confirmed best overall response rate assessed by an independent review committee (IRC) using RECIST 1.1 criteria was 52.3% (complete response 2.3%, partial response 50%). Median duration of response was 6.5 months, range 1.4-9 months. The Kaplan-Meier estimate of 6-month survival was 77%. Median survival was not reached. Median PFS was 6.1 months.
- In the melanoma extension cohort of Study PLX06-02, untreated or previously treated patients with BRAF V600E mutation-positive Stage IV melanoma received vemurafenib (Zelboraf) tablets 960 mg bd (n=32). The median age of subjects was 52 years (range 22-83). ECOG performance status was 0 or 1. Treatment was continued until disease progression. The median (range) duration of treatment was 8.8 months, (0.9-14.6). Confirmed best overall response rate assessed by the

investigator using RECIST 1.1 criteria was 56.3% (complete response 9.4%, partial response 46.9%). Median duration of response was 7.6 months, range 2.9-11.1+ months. The Kaplan-Meier estimates of 6 month and 1 year survival were 87% and 57% respectively. Median survival was not reached. Median PFS was 7.8 months.

Safety

- Safety data was available from 584 patients who received vemurafenib. The major safety data was from the pivotal Study NO25026 (n=336) and the pooled Studys NP22657 and PLX06-02 (n=164). Other data was from 84 patients in clinical pharmacology studies. Most patients received a dose of 960 mg bd. The median duration of treatment was 3.1 months, range 0-9.3 months, in trial NO25026 and 6.4 months, range 0.1-13.7 months, in the pooled trials NP22657 and PLX06-02. The duration of exposure was about 2 months in the other studies.
- In the pivotal trial, the incidence of treatment related adverse events was high and greater with vemurafenib than dacarbazine; 94% for vemurafenib versus 69% for dacarbazine overall, 43% versus 19% for Grade ≥ 3 events, 26% versus 5% for serious adverse events and 38% versus 16% for events requiring dose reduction. Similar high incidences were observed with vemurafenib in the other trials.
- Common treatment related Grade ≥ 3 events with vemurafenib (versus dacarbazine) in the pivotal trial were cutaneous SCC 11.3%, rash 8.3%, keratoacanthoma 6%, arthralgia 3.3%, photosensitivity 2.7%, elevated serum GGT 2.7% and elevated ALP 2.1%. In the dacarbazine group, Grade ≥ 3 SCC was 0.4%, arthralgia 0.7% and the other events 0%. In the pooled trials with longer duration of treatment, the incidence of treatment related Grade ≥ 3 SCC with vemurafenib was even higher at 23%. The corresponding incidences for the other events were rash 6.1%, keratoacanthoma 4.3%, arthralgia 5.5%, photosensitivity 3.7%, elevated serum GGT 8.5% and elevated serum ALP 2.4%. Other common treatment-related Grade ≥ 3 events in the pooled trials included basal cell carcinoma 5.5%, increased serum ALT 4.3% and fatigue 2.4%.
- Adverse events potentially associated with QT prolongation were common across the clinical trials in patients treated with vemurafenib; 8% of patients in the pivotal trial and 9% of patients in the pooled trials. The most common event was dizziness. Grade 3 events were uncommon.
- Based on the Bradford-Hill criteria for causation, the following less common adverse events in clinical trials were possibly related to vemurafenib (sponsor's *Clinical Overview*):
    - Skin: palmar-plantar erythrodysaesthesia syndrome, keratosis pilaris, erythema nodosum, Stevens-Johnson syndrome
    - Musculoskeletal: arthritis
    - Neurological: dizziness, peripheral neuropathy, VIIth nerve paralysis
    - Infections: folliculitis
    - Eye: retinal vein occlusion, uveitis
    - Vascular: vasculitis
    - General: weight loss.
- In the pivotal trial, the vemurafenib dose was reduced mostly because of rash, arthralgia, elevated liver function tests and pyrexia.

- One death (due to tumour lysis syndrome and renal failure) in the clinical trials was possibly related to vemurafenib.

The evaluator supported registration.

Risk management plan

- Implementation of the RMP version 1.0 dated May 2011 and subsequent revisions is recommended as a condition of registration.

Risk-benefit analysis

Delegate considerations

The pivotal Study NO25026 showed that vemurafenib significantly increased overall and progression-free survival compared with dacarbazine in BRAF V600E mutation positive unresectable Stage IIIC or IV melanoma. The data specifically relate to patients with tumours with the V600E mutation which the cobas test was designed to detect. Median follow-up was short. Based on the preliminary data, the median increase in overall survival was 1.4 months and progression-free survival 3.7 months compared with dacarbazine. There is potential for bias in progression-free survival since the trial was open label and there was no independent radiological review. However, there was support from one of the uncontrolled trials NP22657 which did have independent radiological review. The duration of response was short (median around 6 months). Further follow-up is needed to confirm the survival benefit. The US FDA has required an analysis of overall survival after a minimum 24 months follow-up as a post market commitment.

There were limited data on the efficacy and safety of vemurafenib in patients having tumours with other V600 mutations that tested positive on the cobas test.

Vemurafenib was associated with significant toxicity. Serious commonly occurring adverse reactions were cutaneous SCC, rash, arthralgia, photosensitivity, liver dysfunction and reactions associated with electrocardiographic QT prolongation. Skin effects and QT prolongation also occur with the related drug sorafenib. The duration of vemurafenib treatment and follow-up was short. The adverse reactions will require close monitoring and appropriate management. Dose reduction and discontinuation of treatment may be required. In regard to photosensitivity, protective measures against sun exposure are recommended. The Delegate recommended that the precautionary statements in the PI be updated in line with the US product label information.

In conclusion, vemurafenib provided a small survival advantage over dacarbazine and was associated with some significant adverse effects. The benefit-risk balance is marginally in favour of approval but needs to be clarified with longer-term data. Vemurafenib is the first member of a new drug class for metastatic melanoma and provides an alternative for the treatment of some patients with this disease. The Delegate recommended that the indication be restricted to patients with the BRAF V600E mutation as in the trials.

Delegate's draft decision

The Delegate proposed to approve vemurafenib tablets 240 mg (Zelboraf) for the indication:

> *Treatment of unresectable stage IIIC or stage IV metastatic melanoma positive for the BRAF V600E mutation.*

Approval would be subject to finalisation of the Australian PI.

Proposed conditions of registration:

- Implement RMP version 1.0 dated May 2011 and subsequent revisions as agreed with the Office of Product Review.
- Limit unspecified impurities in the drug substance (unless otherwise justified by sponsor).

- Submit 24 month survival and safety data from Study NO25026 when available.
- Submit results of the food-effect study when available.
- Submit results of the study in hepatic impairment when available.

The application was submitted to the Advisory Committee on Prescription Medicines (ACPM) for advice.

Response from sponsor

Comment on the Delegate's proposed action

The sponsor agreed with the Delegate's proposed action to approve Zelboraf (vemurafenib) 240 film-coated tablets.

With regards to the statement from the Delegate that "the risk benefit balance is marginally in favour of approval but needs to be clarified with long term data", Roche commented that a clinically meaningful and statistically significant benefit of vemurafenib treatment on overall survival compared to dacarbazine was demonstrated in the Clinical Study Report (CSR) analysis (December 30, 2010 cut-off). Taken together, the efficacy and safety of vemurafenib demonstrated in the randomised controlled Phase III trial supports a positive benefit-risk assessment in a population with high unmet medical need. Phase I and II studies of vemurafenib in metastatic melanoma patients provide support for this assessment. Additionally, the safety data from the clinical development program indicate that vemurafenib has a well characterised and manageable safety profile. Confirming this positive risk benefit profile, long term data will be provided to TGA as part of the Core Data Sheet updates and as committed to as part of the proposed conditions of registration.

The sponsor disagreed with the Delegate's proposal to restrict the use of Zelboraf to patients positive for the BRAF V600E mutation only. The sponsor considers that the clinical and nonclinical data support the use of the product with BRAF V600 mutations and proposes to change the indication proposed in the submission to make this clear:

> *"Zelboraf is indicated for the treatment of unresectable stage IIIC or stage IV metastatic melanoma positive for ~~the~~ a BRAF V600 mutation".*

The rationale supporting this indication is provided below:

Existing literature indicates that V600E, V600K, V600D and V600R represent >99% of the metastatic melanoma cases with BRAF V600 mutations. The available nonclinical and clinical data suggest efficacy of vemurafenib against tumours with V600 non-E mutations. These data are summarised below followed by a proposal to provide further sequencing data from the pivotal study.

1. Prevalence of V600 Non-E mutations in melanoma

The public Catalog of Somatic Mutations in Cancer (COSMIC) database[25] catalogues entries from published reports of BRAF mutations among various cancers. As of July 2011, among 2099 melanoma specimens with sufficiently characterised BRAF mutations at codon 600, four types of mutations were observed more than once. As noted in Table 30, V600E (1799T>A) was the most frequently identified mutation. V600K was the second most frequent codon 600 mutation, followed by V600R, and a rare 2-base change that results in V600E (denoted V600E2 hereafter). Three other mutations (V600D, V600G and V600M) were each reported only once. Another case of V600G and a single case of V600A were observed in benign melanocytic nevi.

[25] http://www.sanger.ac.uk/perl/genetics/CGP/cosmic

In support of validating the cobas test which was used to select patients for the Phase II and Phase III clinical studies, Sanger sequencing data was collected retrospectively for 496 specimens submitted for Phase III eligibility testing. As shown in Table 30, the results are consistent with expectations based upon the COSMIC database in that among V600 non-E mutations; only V600K, V600D and V600R were observed.

Table 30. Codon 600 BRAF mutations in melanoma

BRAF Codon 600 (Nucleotide sequence)[a]	Anticipated Frequency in V600 Mutation-positive Melanoma[b]	Observed Frequency Among V600 Mutation-positive Specimens Screened for BRIM3[c]
V600E (GAG)	92.5%	81.2%
V600K (AAG)	5.6%	13.4%
V600R (AGG)	1.0%	1.0%
V600E"2" (GAA)	0.7%	4.1%
V600D (GAT, GAC)	<0.1%	0.3%
V600G (GGG), V600M (ATG)	<0.1%	Not observed
V600A (GCG)	0	Not observed

[a] Wild-type nucleotide sequence is GTG.
[b] Estimated from 2099 melanomas with annotated BRAF codon 600 mutations in the public COSMIC database, release 54 (July 2011).
[c] Retrospective sequencing of a subset of 496 specimens screened for entry to BRIM3 identified 314 with BRAF codon 600 mutations.

2. Nonclinical information on efficacy of vemurafenib for V600 Non-E mutations

Nonclinical data generated in biochemical assays demonstrated that vemurafenib can potently inhibit BRAF kinases with activating codon 600 mutations, including V600E, K, D and R-mutant kinases (Table 31) and this inhibitory effect was confirmed in the ERK phosphorylation and cellular anti-proliferation assays in melanoma cells expressing V600E-, V600K-, V600D- and V600R-mutant BRAF. Therefore, the data generated in the nonclinical biochemical assay appear to reliably predict efficacy on BRAF V600 mutants other than V600E. Cell lines bearing rare mutations such as V600A, V600G and V600M are not available for comparison. Table 30 shows that V600E, V600K, V600D and V600R represent >99.5% of the metastatic melanoma cases with BRAF V600 mutations.

Table 31. Kinase inhibitory activity of vermurafenib against V600 mutated BRAF kinases.

Kinase	Source	IC_{50} (nM)
BRAFV600E	Baculovirus	10
BRAFV600E	E. coli	9
BRAFV600K	Baculovirus	7
BRAFV600R	Baculovirus	9
BRAFV600D	E. coli	7
BRAFV600G	Baculovirus	8
BRAFV600A	Baculovirus	14
BRAFV600M	Baculovirus	7

Note: ATP concentration used was 100 uM. Mutant kinases were obtained from two expression systems; IC_{50} values for BRAFV600E indicate that the observed kinase inhibitory activity is independent of source.

In silico protein structure modelling similarly suggests that vemurafenib should inhibit all BRAF V600 mutants. As shown in Figure 26, valine (V) at amino acid position 600 stabilises the inactive conformation of BRAF. Amino acid substitutions for valine which are disruptive induce BRAF to adopt its active conformation, which in turn favours binding of vemurafenib. Figure 26 notes how the inactive conformation is disrupted by the properties of amino acids glutamic acid (E), lysine (K), arginine (R), aspartic acid (D), alanine (A), glycine (G) and methionine (M), among others. Figure 27 highlights the interaction and illustrates how V600E and V600D interact with the αC helix, while V600K and V600R interact with the αE helix. The nonclinical data predict that vemurafenib would inhibit mutant BRAF kinases bearing activating mutations other than V600E and would be effective against tumours bearing such mutations.

3. Summary of available data supporting clinical efficacy in patients with V600 Non-E mutations

Tumour specimens from the PLX06-02 melanoma treatment extension cohort (32 patients), NP22657 (132 patients), and NO25026 (220 patients) studies were retrospectively analysed by Sanger sequencing to investigate the presence of BRAF V600 non-E mutations. Sequencing was also performed on available tumour specimens for patients screened by the cobas test for the Phase II and Phase III trials as of June 15, 2010. A total of 30 patients with V600 non-E mutation-positive melanoma were identified (29 V600K, 1 other which was an unusual V600D mutation and therefore reported as "other"), of whom 20 patients with V600K mutation-positive melanoma received vemurafenib:

PLX06-02 melanoma extension cohort (Phase I): One of 32 patients had BRAF V600 non-E mutation-positive melanoma (V600K) and responded to vemurafenib (960 mg, MBP formulation). This patient had a PFS of 350 days, OS of 392 days and duration of response of 232 days.[26]

NP22657 (Phase II): Nine of the 132 patients had BRAF V600 non-E mutation-positive melanoma by Sanger sequencing, all of which were V600K mutations. Amongst these patients, 3 had a PR, 3 had SD, 2 had progressive disease and one was not evaluable.[27]

[26] Reference: PLX06-02 Clinical Study Report (CSR), BRAF V600 Mutation Screening of Tumors, section 3.3 Retrospective Sequence Analyses.

[27] Reference: NP22657 CSR

NO25026 (Phase III): Twenty of 220 patients were identified to have BRAF V600 non-E mutation-positive melanoma (19 V600K and 1 V600D BRAF mutation). In the vemurafenib group, 4 of 10 patients with BRAF V600K mutation-positive melanoma experienced a treatment response. In the DTIC treatment group, 0 of 9 patients with BRAF V600K mutation positive melanoma and 0 of 1 with BRAF V600D mutation-positive melanoma responded to treatment.[28]

In patients with V600K mutation-positive melanoma, PFS (HR 0.09, 95% CI, 0.02, 0.45) and OS (HR 0.27; 95% CI: 0.05, 1.51) results were suggestive of a treatment benefit of vemurafenib in this subset of 19 patients.[29]

Adverse events observed in patients with the V600K mutation-positive melanoma are summarised in NO25026 CSR. The available clinical data on V600K mutation-positive cases are consistent with the nonclinical data predicting that vemurafenib would inhibit V600 non-E mutant BRAF kinases and would be effective against tumours bearing such mutations.

4. Further evidence of clinical efficacy for V600 Non-E mutations

Roche is performing sequencing on remaining specimens from Study NO25026 (n = 455) to further explore efficacy in patients with V600K mutation-positive melanoma and other V600 non-E mutations. We may be able to identify an additional 30 to 35 patients with BRAF non-E mutation-positive melanoma (primarily V600K). Results from the additional sequencing will be provided as updated information for the entirety of samples from Study NO25026. In total, the report (second quarter of 2012) will include approximately 50 to 55 patients with BRAF V600K mutation-positive melanoma (including 19 of 220 patients with V600K mutation-positive melanoma who were previously identified). OS, PFS and ORR will be reported for each type of BRAF mutation as was done for the NO25026 CSR.

Based on the results from vemurafenib trials in patients with metastatic melanoma, similar anti-tumour activity is expected for vemurafenib in across the spectrum of BRAF V600 non-E mutation-positive tumours. Roche expects the additional sequencing results from the pivotal study will provide further evidence of clinical efficacy in this subpopulation.

In addition, Roche has initiated a Phase IV Study ML27763 “An open label multicenter Phase II study of continuous oral vemurafenib in patients with metastatic melanoma and BRAF mutation not detected by cobas® 4800 BRAF V600 Mutation Test”. Roche proposed to amend the current eligibility criteria to specify that Sanger sequencing to identify other BRAF V600 mutations will be conducted by a central commercial laboratory. Roche is committing to provide any publication from this study to the TGA at the end of 2015.

[28] Reference: NO25026 CSR, Table 31 BORR by BRAF V600E Mutation Status.

[29] Reference: NO25026 CSR.

Figure 26. *In silico* Protein Structure Modelling of Vemurafenib and V600 Mutants

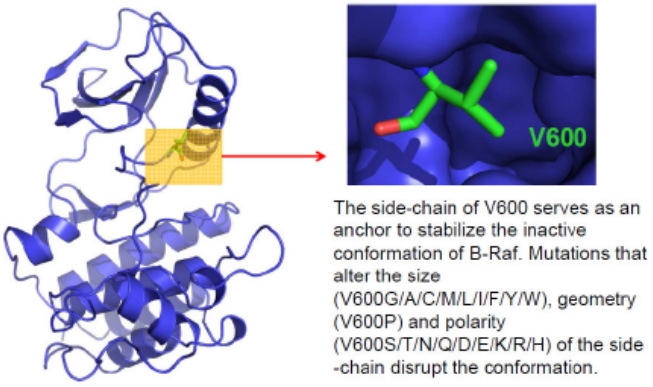
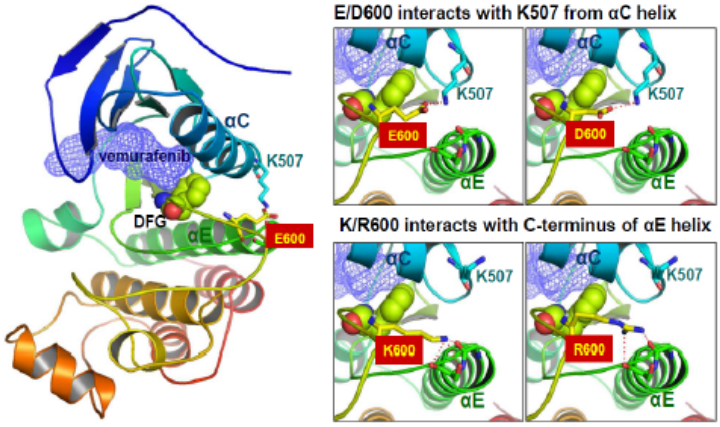


Figure 27. Detailed Interactions between Vemurafenib and BRAF V600 Mutation



Nonclinical and clinical data indicate that vemurafenib is effective against all V600 mutations.

The non-V600E mutations occur too infrequently to study in a rigorous statistical manner; however, nonclinical data and results from patients across the three safety and efficacy studies show there is consistency in responsiveness of the small number of patients with other V600 mutations.

Comment on the Delegate's overview and proposed conditions of registration:

The sponsor stated that while an absolute bioavailability study was not included with the current submission, the sponsor will be conducting an absolute bioavailability study following the development of an intravenous microdose formulation of vemurafenib containing ^{14}C-labeled drug substance. A CSR for this study is anticipated to be available in second quarter of 2014. The sponsor committed to providing the CSR to TGA once it is available.

The Delegate proposed the following conditions of registration in the Delegate's Overview:

1. Implement RMP version 1.0 dated May 2011 and subsequent revisions as agreed with the Office of Product Review.

The sponsor committed to this condition.

2. Limit unspecified impurities in the drug substance (unless otherwise justified by sponsor).

Roche accepted to limit unspecified impurities in the drug substance (R05185426-006). As a consequence, the unspecified impurities in the drug substance intermediate R05185426-000 has also been limited.

3. Submit 24 month survival and safety data from trial N025026 when available.

Roche would like to propose to submit to TGA long term survival and safety data from trial NO25026 as agreed upon with the FDA. Roche would therefore propose to address this commitment as follows:

- Submit in third quarter of 2013 updated overall survival results from the ongoing trial (Protocol N025026: BRIM3) with a minimum follow-up of 24 months after the last patient was enrolled into the trial (cut-off = 12/2012).
- Submit in fourth quarter of 2014 the final analysis of safety from the ongoing trial (Protocol N025026: BRIM3) to provide the potential for new safety signals from longer duration of exposure (cut-off = 03/2014).

4. Submit results of the food-effect study when available.

Results of the food effect study will be submitted in second quarter of 2012.

5. Submit results of the study in hepatic impairment when available.

Results of the study in hepatic impairment will be submitted in third quarter of 2017.

Advisory committee considerations

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

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered this product to have an overall positive *benefit–risk profile* for the following indication**:**

Treatment of unresectable stage IIIC or stage IV metastatic melanoma positive for the BRAF V600 mutation.

In making this recommendation the ACPM noted the significant initial efficacy but cautioned that there was no evidence of significant prolongation of overall survival. The ACPM discussed the evidence to support the proposed indication and agreed with the Delegate that the efficacy and safety had only been established for the V600E mutation and therefore the indication should be similarly restricted. However, the ACPM advised the TGA to investigate the sensitivity of the Cobas 4800 BRAF V600 test to confirm if it is feasible to restrict the indication to the V600E mutation to match the efficacy evidence.

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on inclusion of the following:

- Inclusion in the appropriate section of the CMI a statement to ensure that the evidence of the development of secondary cutaneous squamous-cell carcinomas, as early as in first month of therapy is highlighted.
- Inclusion of information in the appropriate section of the PI to support prescriber awareness of the efficacy and safety for V600E mutations only.

The ACPM agreed with the Delegate on the proposed conditions of registration and supported the consideration of the adequacy of the testing mechanisms and the specificity for the V600E mutation.

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Zelboraf Vemurafenib 240 mg film-coated tablet blister pack, indicated for:

> *"The treatment of unresectable stage IIIC or stage IV metastatic melanoma positive for a BRAF V600 mutation."*

Specific conditions of registration applying to these Therapeutic Goods

1. The implementation in Australia of the Vemurafenib Risk Management Plan (RMP), version 1.0, dated May 2011, included with this submission, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.
2. Submission of the results of ongoing trials to the TGA according to Roche's commitment in their Pre ACPM Response dated 2 March 2012.

Attachment 1. Product Information

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

Therapeutic Goods Administration

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