24 September 2015
EMA/685908/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cotellic

International non-proprietary name: cobimetinib

Procedure No. EMEA/H/C/003960/0000

Note

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

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List of abbreviations

14/14	14 days on/14 days off
21/7	21 days on/7 days off
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	alanine transaminase
API	active pharmaceutical ingredient
AR	assessment report
AST	aspartate transaminase
AUC	area-under-curve
BA	bioavailability
BCS	bioequivalence classification system
BID	twice daily
BORR	best objective response rate
BRAFi	BRAF inhibitor
BRAFi-PD	progressed on prior BRAFi
BRIM2	Alternate study name for NP22657
BRIM3	Alternate study name for NO25026
BRIM7	Alternate study name for NO25395
CHMP	Committee for Medicinal Products for Human Use
CFU	Colony Forming Units
CI	confidence interval
Cmax	maximal concentration
CL	Clearance
CNS	central nervous system
coBRIM	Alternate study name for GO28141
CPK	creatine phosphokinase
CPP	Critical process parameter

CQA	Critical Quality Attribute
CR	complete response
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
cuSCC	cutaneous squamous cell carcinoma
CYP	cytochrome P450
DDI	drug-drug interaction
DLT	dose limiting toxicity
DoE	design of experiments
DOR	duration of response
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency
EU	European Union
F	Bioavailability
FDA	US Food and Drug Administration
FDG PET	18F fluorodeoxyglucose-positron emission tomography
FMEA	Failure mode effects analysis
GC	gas chromatography
HPLC	high pressure liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	in-process control
IR	Infrared
IRC	Independent Review Committee
KF	Karl Fischer titration
LBM	lean body mass
LDH	lactate dehydrogenase
LOD	Loss on drying
LVEF	left ventricular ejection fraction

MAA	Marketing Authorization Application
MAPK	mitogen activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximal tolerated dose
NCI	National Cancer Institute
NMR	Nuclear Magnetic Resonance
NMT	Not more than
ORR	objective response rate
OS	overall survival
PAR	Proven Acceptable Range
PBPK	Physiologically based pharmacokinetics
PD	progressive disease
PET	Positron emission tomography
PFS	progression free survival
Ph.Eur.	European Pharmacopoeia
PIB	powder in bottles
PIC	powder in capsule
PK	Pharmacokinetic
PPI	proton-pump inhibitor
PR	partial response
PTP therapy	previously treated patients but without prior exposure to any BRAF or MEK inhibitor
PUP	previously untreated patients
PVC	Poly vinyl chloride
PVDC	Polyvinylidene chloride
QbD	Quality by design
QD	once daily
QTc	QT interval (time between start of the Q wave and end of the T wave) corrected
QTPP	Quality target product profile
RECIST	Response Evaluation Criteria in Solid Tumours
RH	Relative Humidity
RMP	risk management plan

RVO	retinal vein occlusion
SAE	serious adverse event
SCC	squamous cell carcinoma
SD	stable disease
SmPC	Summary of Product Characteristics
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
Vemurafenib-PD	progressed on prior treatment with vemurafenib monotherapy

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration Ltd submitted on 2 September 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Cotellic, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 February 2014.

The applicant applied for the following indication: Cotellic is indicated for use in combination with Zelboraf (vemurafenib) for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

The legal basis for this application refers to:

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

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0025/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0025/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

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

Scientific Advice

The applicant received Scientific Advice from the CHMP on 27 June 2013 and 25 April 2014. The Scientific Advice pertained to quality and clinical aspects of the dossier.

Licensing status

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

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Daniel Brasseur

- The application was received by the EMA on 2 September 2014.
- The procedure started on 24 September 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 December 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 17 December 2014.
- During the meeting on 9 January 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 22 January 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 January 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 April 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 June 2015.
- During the meeting on 11 June 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the CHMP meeting on 25 June 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 August 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 September 2015.
- During the meeting on 10 September 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 24 September 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Cotellic.

2. Scientific discussion

2.1. Introduction

Cutaneous melanoma is the most aggressive form of all skin cancers. An estimated 85294 people will be diagnosed with melanoma in 2015 in the EU, and approximately 16630 people are expected to die

of the disease annually[1]. The survival for stage IV melanoma patients has been historically poor, with a 5 year survival rate of approximately 10% and a median survival of 6-10 months[2].

The RAS/RAF/MEK/ERK pathway (i.e., the mitogen-activated protein kinase [MAPK] pathway) is a critical pathway involved in the proliferation of normal cells as well as in many human cancers. The pathway affects many cancers, in particular melanoma where approximately 50% of cutaneous malignant melanomas have specific mutations of the BRAF-oncogene which constitutively activate MEK[3] . The BRAF mutation most frequently found in melanoma was shown to be V600 (74-90%)[4]. This oncogenic mutation at the V600 site in BRAF leads to constitutive activation of the RAS/RAF/MEK/ERK pathway.

There are currently two small molecule inhibitors of BRAFV600, vemurafenib (Zelboraf) and dabrafenib (Tafinlar), and one small molecule inhibitor of MEK, trametinib (Mekinist) that have been approved as monotherapy for the treatment of adult patients with unresectable or metastatic melanoma that harbour the BRAF V600 mutation. More recently, the combination of trametinib (Mekinist) and dabrafenib (Tafinlar) has been authorised in the same indication.

The approval of vemurafenib was based on a pivotal phase III study (BRIM3) which demonstrated clinical benefit with regard to overall survival (OS) (HR=0.37; p<0.001) and progression free survival (PFS) (HR=0.26; p<0.001) as compared with DTIC in patients with metastatic melanoma with a BRAF V600E mutation[5].

The approval of dabrafenib was based on the pivotal phase III BRF113683 study in which the efficacy and safety of dabrafenib was compared with DTIC. In this study, a statistically significant improvement in PFS (HR 0.37; 95% CI 0.24, 0.58; p<0.0001) was seen where median PFS for dabrafenib was 6.9 months compared to 2.7 months with DTIC. The median OS for dabrafenib was 20.0 months in comparison to 15.6 months for DTIC (HR 0.77; 95% CI 0.52, 1.13).

The pivotal study for the approval of trametinib was a phase III study MEK114267 where the median PFS was 4.8 months for patients treated with trametinib and 1.5 months for patients treated with chemotherapy (HR 0.45; 95% CI 0.33, 0.63; p<0.0001). The median OS was 15.6 and 11.3 months for patients in the trametinib and chemotherapy arms respectively (HR 0.78; 95%CI 0.57,1.06).

Other treatment options have been approved for melanoma in recent times, namely treatments that target the immune system instead of targeting the cancer itself. In 2011, the anti-CTLA-4 antibody ipilimumab (Yervoy) was approved for the treatment of advanced (unresectable or metastatic) melanoma in adults. Ipilimumab, a monoclonal antibody that blocks the cytotoxic T-lymphocyte antigen CTLA-4, has demonstrated a significant improvement (hazard ratio [HR]=0.68, p<0.001) in overall survival (OS) compared with gp100 peptide vaccine in previously treated patients with metastatic melanoma[6]. More recently, additional immunotherapeutic options available include the monoclonal antibodies nivolumab (Opdivo) and pembrolizumab (Keytruda) for the treatment of advanced (unresectable or metastatic) melanoma in adults.

As observed in the pivotal studies, the clinical benefit of monotherapy with BRAF and MEK inhibitors appears to be limited by the development of resistance, with approximately 50% of the patients treated with BRAF inhibitors progress within 5 to 7 months after starting treatment and the vast majority of patients with BRAF-mutated melanoma eventually will die from the disease in in less than 18 months[5, 7, 8 , 9, 10]. Although several mechanisms of acquired resistance to BRAF and MEK inhibitors that have been proposed[11, 12], the main pathway for resistance is thought to be the reactivation of the MAPK pathway through alternative activation of downstream MEK[13, 14] . Thus, cobimetinib and vemurafenib combination would inhibit the same pathway but at different levels, MEK and BRAF, and

provide concomitant inhibition of the same pathway. It is suggested that inhibiting both MEK and BRAF simultaneously could postpone or possibly prevent the development of resistance[15, 16, 17, 18, 19, 20].

Cobimetinib is a reversible, selective, allosteric, oral inhibitor that blocks the mitogen-activated protein kinases (MAPK) pathway by targeting the mitogen-activated extracellular signal regulated kinase (MEK) 1 and MEK 2 which results in inhibition of phosphorylation of the extracellular signal-related kinase (ERK) 1 and ERK 2. Therefore, cobimetinib blocks the cell proliferation induced by the MAPK pathway through inhibition of the MEK1/2 signalling node.

In the preclinical models, the combination of cobimetinib and vemurafenib showed that by simultaneously targeting mutated BRAF V600 proteins and MEK proteins in melanoma cells, the combination of the two products inhibits MAPK pathway reactivation through MEK1/2, resulting in a stronger inhibition of intracellular signalling and decreased tumour cell proliferation

The applicant applied for the following indication:

Cobimetinib is indicated for use in combination with Zelboraf (vemurafenib) for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma (see section 5.1).

The final approved indication is as follows:

Cotellic is indicated for use in combination with vemurafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see sections 4.4 and 5.1).

Treatment with Cotellic in combination with vemurafenib should only be initiated and supervised by a qualified physician experienced in the use of anticancer medicinal products.

Before starting this treatment, patients must have BRAF V600 mutation-positive melanoma tumour status confirmed by a validated test (see sections 4.4 and 5.1).

Posology

The recommended dose of Cotellic is 60 mg (3 tablets of 20 mg) once daily.

Cotellic is taken on a 28 day cycle. Each dose consists of three 20 mg tablets (60 mg) and should be taken once daily for 21 consecutive days (Days 1 to 21-treatment period); followed by a 7-day break (Days 22 to 28-treatment break). Each subsequent Cotellic treatment cycle should start after the 7-day treatment break has elapsed (SmPC section 4.2).

For information on the posology of vemurafenib, please refer to its SmPC.

Treatment with Cotellic should continue until the patient no longer derives benefit or until the development of unacceptable toxicity. If a dose is missed, it can be taken up to 12 hours prior to the next dose to maintain the once-daily regimen. In case of vomiting after administration of Cotellic, the patient should not take an additional dose on that day and treatment should be continued as prescribed the following day (SmPC section 4.2).

Cotellic is for oral use. The tablets should be swallowed whole with water. They can be taken with or without food (SmPC section 4.2).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a film-coated tablet containing cobimetinib hemifumarate equivalent to 20 mg cobimetinib as active substance.

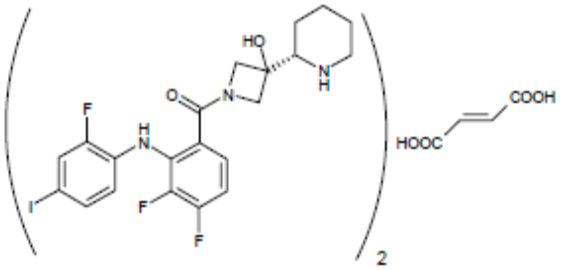
Other ingredients are for tablet core: lactose monohydrate, microcrystalline cellulose (E460), croscarmellose sodium (E468), magnesium stearate (E470b) and for film coating: polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc (E553b).

The product is available in transparent PVC/PVDC blisters containing 21 tablets as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of cobimetinib hemifumarate is (*S*)-[3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl] [3-hydroxy-3-(piperidin-2-yl)azetidin-1-yl]methanone hemifumarate and it has the following structure:



The active substance is a non-hygroscopic white to off-white solid. The solubility is high over the pH range 1 to 7.5.

Manufacture, characterisation and process controls

The active substance is sourced from one supplier involving two manufacturing sites.

The active substance is synthesized in seven steps with a telescoped part of five non-isolated steps. The last step is salt formation. An optional re-working procedure is described and is considered acceptable. The synthesis uses commercially available well defined starting materials with acceptable specifications. The active substance has one chiral centre which has the (S)-configuration. Enantiomeric purity is controlled by the manufacturing process and starting material specifications. In addition enantiomeric purity is controlled routinely by chiral HPLC control in the active substance specifications. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The same synthetic route has been used throughout the development from toxicological studies to the commercial batches. Changes introduced during development of active substance manufacturing process have been presented in sufficient detail and have been justified. The development of the manufacturing process is based on the combination of a traditional and enhanced approach (ICHQ11, ICHQ8, ICHQ9).

The active substance Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs) are described.

Moreover, critical material attributes have been defined for starting material and intermediates.

The manufacturing process has been developed using a combination of conventional univariate studies and elements of QbD such as risk assessment, design of experiment (DoE) studies. Based on these studies, proven acceptable ranges (PARs) have been defined for several steps of the manufacturing

process of the active substance. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs. Confirmation is provided that no design space is claimed.

The chemical structure of cobimetinib is confirmed by using elemental analysis, infrared spectroscopy, NMR spectroscopy (^{1}H, ^{13}C & ^{13}C solid-state), mass spectrometry, single crystal X-ray diffraction and UV spectroscopy. Polymorphism has been observed for the active substance. Cobimetinib exists in two solid forms. The same polymorphic form is consistently produced by the manufacturing process. Polymorphic form of the active substance is also controlled in the active substance specifications. A comprehensive list of impurities that may arise from the synthesis (starting materials, solvents, reagents, intermediates, by-products, genotoxic impurities) or from degradation is discussed. The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances.

The active substance is packaged in closed, double low-density polyethylene bags within a closed steel drum. The low-density polyethylene bags comply with the EC directive 2002/72/EC.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC), assay (HPLC), fumaric acid content (HPLC), impurities (HPLC), enantiomeric content (HPLC), genotoxic impurities (GC), residual solvents (GC), water content (KF), heavy metals (USP), palladium (USP), particle size distribution (laser diffraction), residue on ignition (USP) and polymorphic form (X-ray powder diffraction).

The control strategy for genotoxic impurities was discussed in a recent scientific advice, EMEA/CHMP/SAWP/210707/2014, and the applicant has followed the advice. The control strategy is thus considered acceptable.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on ten pilot scale batches of active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data were provided on five batches of active substance (three primary stability batches, including one production scale batch, and two supportive stability batches) manufactured by the proposed manufacturer according to earlier development manufacturing process. The differences between the manufacturing process for the three primary stability batches and that of the commercial manufacturing process are considered not to be relevant in terms of potential impact on the stability profile. Stability batches were stored in the intended commercial package for up 24 to months under long term conditions at 30 °C / 75% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines.

The following parameters were tested: appearance; water content; assay; impurities; enantiomeric purity; particle size; polymorphic form. The analytical methods used were the same as for release and are stability indicating. All tested parameters were within the specifications.

Photostability testing following the ICH guideline Q1B was performed on one batch. Forced degradation studies have also been performed. Results demonstrate that the active substance in the solid state is not sensitive to light, elevated temperature or humidity.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 30 months below 30 °C in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of the pharmaceutical development was to develop an immediate-release film-coated tablet containing cobimetinib.

The composition of the finished product is provided.

The pharmaceutical development includes elements of science and risk-based approaches such as described in ICH Q8(R2) and ICH Q9.

A QTPP was established which forms the basis for the finished product development. CQAs were identified. Finished product CQAs are appearance, cobimetinib content, degradation products, uniformity of dosage units, dissolution and microbial limits.

The hemifumarate salt of cobimetinib was selected since it exists in only one crystalline form with a high melting point and low hygroscopicity. Conversion to the amorphous state during tablet production is very unlikely due to the high melting point.

Appropriate active substance particle size distribution criteria are defined to ensure satisfactory finished product processability and performance.

A number of standard excipients were examined for their compatibility with the active substance by testing binary mixtures of active substance and excipient in accelerated/stressed stability studies. Suitable excipients were further investigated for compatibility between excipients themselves. All excipients selected are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The amount of each excipient is justified as well.

An assessment of the benefits of dry and wet granulation was made initially and due to the simplicity of the process (reduced number of unit operations), dry granulation by roller compaction was chosen for development.

The formulation development used risk assessment and DoE studies to find an appropriate phase III and commercial formulation.

Two tablet formulations have been used during clinical development. The proposed commercial formulation was already used for phase III studies. Based on bioequivalence studies against the phase I formulation bridging between the prototype and the commercial tablet can be accepted.

The manufacturing process has been developed using a combination of conventional univariate studies and elements of QbD such as risk assessment and DoE studies. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The critical process parameters have been adequately identified.

Description of the development of the dissolution method is provided. The discriminatory power of the dissolution method developed for quality control has been demonstrated. However, based on the high

solubility of the active substance and rapid dissolution, a correlation with *in vivo* exposure is not possible.

The primary packaging is a transparent PVC/PVDC blister. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of six main steps: blending, screening, dry-granulation (roller compaction), tablet compression, film-coating, packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated on seven batches including three production scale batches produced at the proposed manufacturing site. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. PARs have been defined for several steps of the medicinal product manufacture. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

Formal validation will be performed post-approval on commercial batches. An acceptable validation plan has been presented.

Product specification

The finished product release specification includes appropriate tests for this kind of dosage form: description, identification (IR, HPLC), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.) and microbial limits (USP, Ph. Eur.).

The absence of tests for water content has been acceptably justified by the applicant.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for several batches including fourteen production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data were provided for 11 batches of finished product (six primary stability batches, including two production scale batches, and five supportive stability batches) stored under long term conditions for up to 24 months at 30 °C / 75% RH and for up to 6 months under accelerated conditions at 40 °C / 75% RH according to the ICH guidelines. The batches of medicinal product are representative to those proposed for marketing and 3 stability batches were packed in the primary packaging proposed for marketing. Differences between stability batches and commercial batches are the debossing which is not considered likely to impact the stability profile.

Samples were tested for appearance, assay, degradation products, dissolution and microbial quality. The analytical methods used were the same as for release and are stability indicating. In addition, water content, hardness, disintegration time, chiral purity, water activity and friability were monitored for better characterization of the finished product stability. A limit test is used for chiral purity and the method description has been provided.

All parameters remained within specification during the stability testing at all storage conditions. No significant changes have been observed.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Results demonstrated that the finished product is not light sensitive.

Based on available stability data, the shelf-life of 24 months with no special storage conditions as stated in the SmPC is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The finished product is presented as a film-coated tablet containing the new active substance cobimetinib hemifumarate. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The applicant has applied QbD principles in the development of the active substance and the finished product and their manufacturing process. Proven acceptable ranges have been defined for several steps of the active substance manufacture and the medicinal product manufacture. However, no design spaces were claimed. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Non-clinical pharmacology, ADME/PK, and toxicology studies submitted were performed in a variety of species. These include mouse, rats and dogs. Pharmacology studies to evaluate the effect of cobimetinib on cancer cells included *in vitro* biochemical and anti-proliferative studies and *in vivo* in mouse xenograph models. PK studies were conducted in mice, rats, dogs, and cynomolgus monkeys. Safety pharmacology studies were performed in vitro in hERG cells and in vivo in rats and dogs. Toxicology studies were performed in rats and dogs.

Primary and secondary pharmacodynamics studies were not performed under GLP as well as for the distribution, metabolism, and excretion studies. However, safety pharmacology studies genotoxicity, embryo-foetal development, juvenile studies, local tolerance study and the phototoxicity studies were performed under GLP. There was no indication of the GLP status of the absorption studies. Single-dose toxicity studies included GLP and non-GLP studies. Non-pivotal repeat-dose toxicity studies were non-GLP, whereas pivotal studies were GLP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro studies

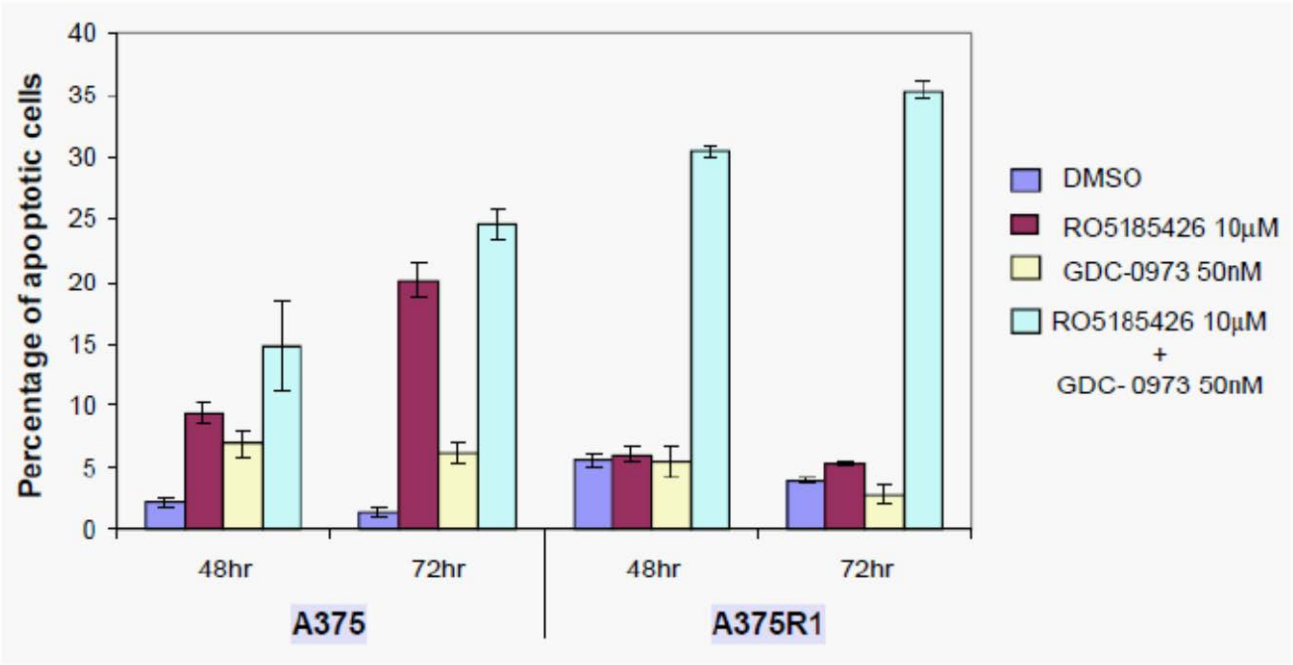
In biochemical assays, cobimetinib was tested against a panel of different tyrosine and serine/threonine kinases. Results are shown in Table 1.

Table 1: Induction of apoptosis following the combination of cobimetinib (GDC-0973) and vemurafenib (RO5185426) in A375 parental and A375R1 cells - Study 1046219

Kinase	Cobimetinib IC50 ± SEM (nM)
MEK1	0.95 ± 0.1
MEK2	199 ± 52
Abl; Akt1; Akt2; ALK; AMPK; ASK1; Aurora-A; B-Raf; B-RafV600E; Btk; CamK2σ; CaMKI; CDK2/cyclinE; CDK6/cyclinD3; CHK1; CHK2; CK1; CK2; CLK3; c-RAF; DAPK1; DYRK2; EGFR; EMK; EphA2; EphA4; EphB4; ErbB2; ERK1, ERK2, FAK; Fes; FGFR1; FGFR3; Flt-1; Flt3; Flt-3; Flt-4; Fms; GRK2; GRK5; GSK3β; Hck; HIPK1; PKA; IGF-1R; IKKα; IRAK1; IRK; JAK2; JNK1; KDR; Kit; Lck; LOK; Lyn; MAP4K3; MAPKAP2; MARK1; Met; MINK; MKK4; MKK6; MKK7β; MLK1; MSK1; MST1; NEK3; NEK7; NLK ; p38α; p70S6K; PAK2; PAK4; PAK6; PASK; PDGFRβ; PDGFRα; PDK1; PI3Kα; PI3Kβ; PI3Kγ; PIM1; PIM2; PIM3; PKCβII; PKCα; PKCγ; PKD2; Plk3; ROCK-I; RON; Rsk1; SGK; SYK; SRC; STK24; Tie-2; TrkB; TSSK1; WNK2; ZAP-70	>10000

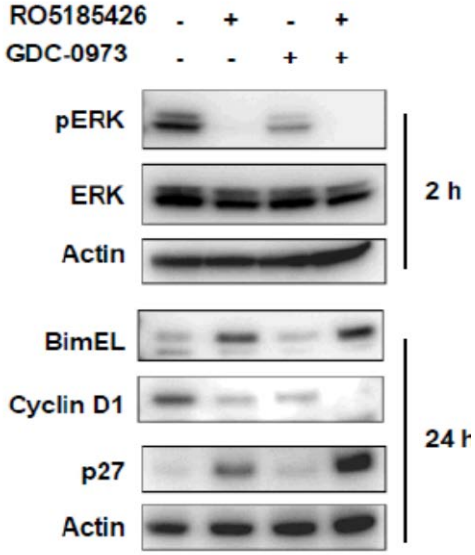
The apoptotic activity of cobimetinib in combination with vemurafenib was evaluated in the parental cell line (A375) and one vemurafenib-resistant cell line (A375R1) using the Annexin V/7-AAD assay 48 and 72 hours after treatment with cobimetinib (GDC-0973) and vemurafenib (RO5185426). The results are presented in Figure 1 and show that the combination of vemurafenib and cobimetinib was able to overcome the resistance observed with either of the compounds alone.

Figure 1: Kinase profile for cobimetinib - Study 13-2987



The pharmacodynamic and phenotypic effects of cobimetinib and vemurafenib were tested in A375 $BRAF^{V600E}$ melanoma cell lines (Figure 2). The results showed that the combination of vemurafenib and cobimetinib inhibited pERK as well as cyclin D1 but increased expression of the BH3-only protein Bcl-2 interacting mediator of cell death, which promotes apoptosis.

Figure 2: Pharmacodynamic effects of cobimetinib and vemurafenib in A375 BRAFV600E melanoma cells, 50 nM cobimetinib (GDC-0973), 10 µM vemurafenib (RO5185426) - Study 1046219



In vivo studies

Subcutaneous xenograft melanoma tumour growth study

Cobimetinib and vemurafenib were tested as single agents or in combination in the A375 BRAFV600E-melanoma xenograft model using the parental cell line (A375) as well as the vemurafenib-resistant cell line (A375R1). The results are presented in Table 2.

Table 2: Summary of in vivo xenograft studies with monotherapy or combination treatment of cobimetinib or vemurafenib in the sensitive parental A375 model and the A375R1 xenograft mouse model with acquired resistance to vemurafenib - Study 1046219

Doses (mg/kg, QD)	A375 Sensitive				A375R1 Resistant			
	TGI	PR	CR	ILS	TGI	PR	CR	ILS
Vemurafenib (25)	108%	9	0	58%	7%	0	0	0%
Cobimetinib (1.5)	115%	5	5	96%	63%	0	0	28%
Cobimetinib (3)	118%	2	8	96%	83%	0	0	26%
Vemurafenib (25) + Cobimetinib (1.5)	119%	0	10	117%	84%	-[a]	0	67%
Vemurafenib (25) + Cobimetinib (3)	118%	0	10	117%	96%	1	0	78%

CR = complete response; ILS = increase in life span; PR = partial response; QD = once a day; TGI = tumour growth inhibition. a The field was blank in the original study report.

Secondary pharmacodynamic studies

Cobimetinib was assessed against a panel of secondary pharmacologic targets including 90 receptors, transporters, and enzymes by in vitro binding assays and enzyme assays. A summary of the noteworthy findings are presented in Table 3.

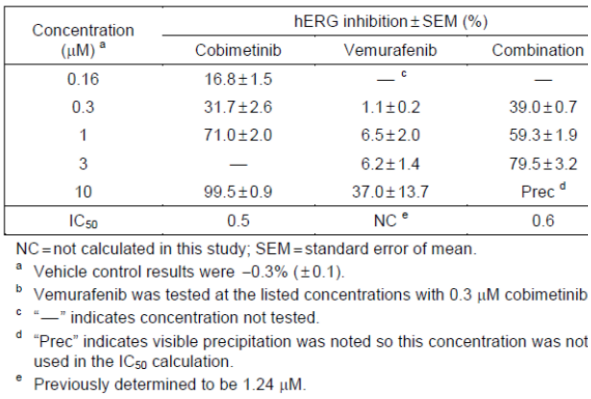
Table 3: Summary of findings from secondary pharmacodynamic studies

Organ/ Systems Evaluated	route	drug	Doses	Noteworthy Findings	GLP	Study ID report nr
Secondary pharmacodynamics	In vitro	cobimetinib	10 uM enzyme and binding assays	Low-potential for secondary pharmacology on receptor, transporter, or ion channel-related responses: 12 off-target receptors, ion channels, and transporters with IC50 from 0.57-10 uM = 21-to 374-fold higher than unbound human Cmax at 60 mg dose (14 ng/ml; 0.03 uM): adrenergic beta 2 receptor (IC50 = 2.0 μM) muscarinic M1 and M2 receptors (IC50 = 8.8 and 10 μM, respectively) opiates mu and kappa receptors (IC50 = 4.80.66 and 0.664.8 μM, respectively) serotonin 5-HT2B receptor (IC50 = 2.0 μM) non-selective sigma receptor (IC50 = 0.71 μM) somatostatin receptor (IC50 = 3.7 μM) sodium channel site 2 (IC50 = 1.9 μM) calcium L-type channels (diltiazem and verapamil sites, IC50 = 0.57 and 6.7 μM, respectively) norepinephrine and dopamine transporters (IC50 = 10 and 7.2 μM, respectively).	No	859001

Safety pharmacology programme

Cobimetinib was evaluated for potential adverse effects on neurobehavioral, cardiovascular, and respiratory system functions in safety pharmacology studies conducted in compliance with GLP regulations. Cobimetinib was also evaluated in studies for the effects on hERG channel activity (GLP) *in vitro* and for inhibitory potential of a broad class of pharmacologically active receptors, enzymes, and channels in vitro (non-GLP). The results are presented in Table 4.

Table 4: Safety pharmacology

Species, Type of study, GLP, Study no	Gender and no/grp	Method of Admin, Duration of dosing	Doses (mg/kg)	Safety pharmacology findings
In vitro, receptor binding and enzyme assays, non-GLP, 859001	NA	NA	10 uM	>50% inhibition of adrenergic beta 2 (IC50 = 2.0 μM); muscarinic M1 and M2 (IC50= 8.8 and 10 μM, respectively); opiates mu and kappa (IC50= 40.66 and 4.8 μM, respectively); serotonin 5-HT2B (IC50 = 2.0 μM); non-selective sigma (IC50= 0.71 μM) and somatostatin receptors (IC50 = 3.7 μM); Na + channel site 2 (IC50 = 1.9 μM); calcium L-type channels (diltiazem and verapamil sites, IC50 = 0.57 and 6.7 μM, respectively); and the norepinephrine and dopamine transporters (IC50= 10 and 7.2 μM, respectively).
In Vitro, hERG, GLP, 12-3641	NA	NA	0.16-10 uM	

Concentration (μM) [a]	hERG inhibition ± SEM (%)		
	Cobimetinib	Vemurafenib	Combination
0.16	16.8±1.5	— [c]	—
0.3	31.7±2.6	1.1±0.2	39.0±0.7
1	71.0±2.0	6.5±2.0	59.3±1.9
3	—	6.2±1.4	79.5±3.2
10	99.5±0.9	37.0±13.7	Prec [d]
IC_{50}	0.5	NC [e]	0.6

NC = not calculated in this study; SEM = standard error of mean.
[a] Vehicle control results were –0.3% (±0.1).
[b] Vemurafenib was tested at the listed concentrations with 0.3 μM cobimetinib
[c] "—" indicates concentration not tested.
[d] "Prec" indicates visible precipitation was noted so this concentration was not used in the IC_{50} calculation.
[e] Previously determined to be 1.24 μM.

In vivo, Irwin, GLP, XL518-NC-006	Rat, 6M	Oral, single dose	0, 7.5, 15, 30	Cobimetinib produced no biologically significant effects on neurobehavioral endpoints in rats up to 30 (unbound C_{max} = 19.5 ng/mL).
In vivo, Respiratory, GLP, XL518-NC-009	Rat, 6M	Oral, single dose	0, 30, 100, 300	Small, gradual decrease in respiratory rate (18% below predose values) at high dose. NOAEL 100 mg/kg (total Cmax = 1910 ng/mL; unbound Cmax = 63.7 ng/mL [0.120 μM]).
In vivo, Cardiovascular, GLP, XL518-NC-010	Dog, 4M	Oral, 4 doses, one week apart	0, 0.3, 1, 3	Cobimetinib did not elicit any biologically significant changes in electrocardiogram, cardiovascular, hemodynamic, or respiratory parameters in dogs up to 3 mg/kg (unbound C_{max} = 5.2 ng/mL) when compared with vehicle treatment.

Pharmacodynamic drug interactions

No pharmacodynamics drug interaction studies have been submitted (see non-clinical discussion).

2.3.3. Pharmacokinetics

Absorption

Studies have been performed to characterise the pharmacokinetics of cobimetinib (absorption, distribution, metabolism and excretion) in dog and rat. The results are presented in Table 5 and Table 6.

Table 5: Absorption after single cobimetinib dose administration

Study ID, GLP	Species	N	Form	Dose (mg/kg), Route	V_{ss} (L/kg)	Cmax (uM)	AUC (uM*h)	t½ (h)	CL (L/kg/h)
RPT_PK_021406-01, non-GLP	Rat	4F	Saline	3, iv	22.6	1.2	2.03	3.8	2.57
			Water	3, po	-	0.14	1.46	5.74	-
			Capsule	3, po	-	0.19	2.40	5.67	-
			Water	10, po	-	0.26	3.51	5.32	-
			Water	30, po	-	0.91	13.3	5.77	-
			Water	100, po	-	3.64	163	NR	-
			Water	300, po	-	8.44	380	NR	-
RPT_PK_013106-01, non-GLP	Dog	3M	Saline	3, iv	3.9	2.13	15.6	8.84	0.33
			Saline	3, po	-	0.76	10.8	8.75	-

Table 6: Toxicokinetic parameters

Study, GLP	Species, n/sex, route of administration, formulation	Dose (mg/kg/day), Regime	Time point (day)	Dose	C_{max} (ng/ml)	AUC_{0-24} (ng*h/ml)	T_{max} (h)
XL518-NC-002, GLP	Rat, 9 M/F, water	30, po, single dose	NA	30M	384	5220	6
				30F	620	8340	8
		75,po, single dose		75M	1060	15400	6
				75F	1140	20300	2
		150, po, single dose		150M	3670	21000	48
				150F	3480	25900	48
		300, po, single dose		300M	6100	38100	48
				300F	8330	72600	48
XL518-NC-003, GLP	Dog, 2 M/F, water	10, po, single dose	NA	10F	1870	29400	3
				10M	1660	24200	4
		30, po, single dose		30F	4690	84400	12.5
				30M	8400	97800	48
		60, po, single dose		60F	11500	140000	36
				60M	8760	127000	24
XL518-NC-004, GLP	Rats, 15 M/F, water	1, 3, 10, po, daily, 4 week + 4 week recovery	1	1F	6.88	106	8
				1M	5.32	76.8	4
				3F	36.6	453	4
				3M	24.3	258	6
				10F	141	1702	6
				10M	96.5	1123	8
			28	1F	12.7	157	4
				1M	10.3	102	4
				3F	55.4	602	2
				3M	28.6	330	6
				10F	851*	12603*	4*
				10M	357	2892	6
XL518-NC-012, GLP	Rat, 15 M/F, water	0.3, 1, 3, po, daily, 13 week+4 week recovery	1	0.3F	1.33	19	6
				0.3M	1.04	14	8
				1F	6.07	67.2	8
				1M	4.74	50.4	4
				3F	24.4	318	6

				3M	17.3	176	8
			45	0.3F	4.93	50	4
				0.3M	1.65	26.9	8
				1F	18.3	185	8
				1M	8.21	101	4
				3F	57.6	749	4
				3M	35.5	389	8
			90	0.3F	4.48	47.4	4
				0.3M	2.19	28.1	2
				1F	17.8	176	4
				1M	9.57	114	4
				3F	77.4	772	2
				3M	41.4	460	4
XL518-N-005, GLP	Dog, 5 M/F, water	0.1, 0.3, 1.0, po, daily, 4 week+4 week recovery	1	0.1F	8.53	91.5	2.67
				0.1M	10.4	107	4
				0.3F	30.8	325	4
				0.3M	21.6	221	5.33
				1F	179	1410	2.6
				1M	206	2060	3.6
			28	0.1F	11.7	107	2.67
				0.1M	15.9	104	2.33
				0.3F	49.4	556	4
				0.3M	34.2	335	2.67
				1F	263	2420	3.2
				1M	343	4060	3.6
XL518-NC-013, GLP	Dog, 5 M/F, water	0.3, 1, 3, po, daily, 13 week+4 week recovery	1	0.3F	47.9	396	2.8
				0.3M	53.6	423	2.4
				1F	221	1460	2.6
				1M	194	1210	2.6
				3F	585	5480	3.3
				3M	602	5470	3.6
			10	3F	892	10400	4
				3M	2310	19300	4.3
			30	0.3F	34.3	362	3.6
				0.3M	52.6	525	4.4
				1F	213	2160	4
				1M	230	2160	4
				3F	ND	ND	ND
				3M	ND	ND	ND
			59	0.3F	29.9	320	4.8
				0.3M	43.5	452	2.8
				1F	253	2220	3
				1M	229	2310	4
				3F	ND	ND	ND
				3M	ND	ND	ND
			90	0.3F	30.5	330	2
				0.3M	46.4	480	2.6
				1F	204	2110	3
				1M	195	2460	4
				3F	ND	ND	ND
				3M	ND	ND	ND

Distribution

The results of in vitro distribution studies for unbound and bound plasma proteins are shown in Table 7 and Table 8.

Table 7: Mean (± SD) percent of [14C]cobimetinib bound and unbound in rat, dog and human plasma - Study 09-0614

Species	Total Cobimetinib Concentration (μM)	Percent Bound [^{14}C] Cobimetinib	Percent Unbound [^{14}C]Cobimetinib
Rat	1	97.2 ± 0.369	2.81 ± 0.369
	5	96.5 ± 0.446	3.55 ± 0.446

	10	96.3 ± 0.274	3.73 ± 0.274
Dog	1	99.3 ± 0.0230	0.663 ± 0.0230
	5	98.8 ± 0.236	1.15 ± 0.236
	10	98.6 ± 0.163	1.41 ± 0.163
Human	1	94.8 ± 0.351	5.19 ± 0.351
	5	93.5 ± 0.355	6.47 ± 0.355
	10	94.2 ± 0.169	5.83 ± 0.169

Table 8: Mean (± SD) blood to plasma ratio and percent recovery of [14C] cobimetinib in rat, dog, and human whole blood - Study 09-0671

Species	Total Cobimetinib Concentration (μM)	Blood–Plasma Ratio of [14C]Cobimetinib
Rat	1	1.36 ± 0.0241
	5	1.37 ± 0.0191
	10	1.51 ± 0.0746
Dog	1	0.632 ± 0.0112
	5	0.752 ± 0.00870
	10	0.936 ± 0.0114
Human	1	0.933 ± 0.0141
	5	0.945 ± 0.00659
	10	1.05 ± 0.0129

At designated times following dosing of oral administration of [14C] cobimetinib, blood and carcasses for whole-body autoradiography (WBA) were collected. The results are shown below (Table 9):

Table 9: Tissue distribution in male Long Evans rats (peak concentrations, only tissue with ng Equivalents 14C-GDC-0973/g > 35500 shown)

Tissue Equivalents	Small intestine 2900000	Stomach contents 1470000	Large intestinal content 755000	Cecum contents 515000	Esophageal contents 172000
	Bile 167000	Liver 93200	Large intestine 60000	Lungs 59700	Adrenal gland 57600
	Urinary bladder 45900	Pituitary gland 44600	Eye uveal tract 39500		

In the eye uveal tract, the highest concentration was observed at 8 hours postdose (39500 ng equivalents/g). By the final sampling time of 672 hours postdose, the uveal tract concentration had declined to 4460 ng equivalents/g. The radioactivity concentration in eye uveal tract at 672 hours postdose represented an approximately 9-fold decrease in radioactivity concentration from the observed peak concentration at 8 hours postdose. The highest concentrations in pigmented skin and non-pigmented skin (5200 and 4440 ng equivalents 14C-GDC-0973/g, respectively) were observed at 4 hours postdose. The radioactivity concentrations in pigmented skin generally declined and dropped to a concentration of 501 ng equivalents/g at 672 hours postdose. The radioactivity concentrations in non-pigmented skin generally declined and dropped to non-detectable levels (ND) by 72 hours postdose.

Table 10: Tissue distribution in male Sprague Dawley rats (peak concentrations, only tissue with ng Equivalents ^{14}C-GDC-0973/g > 24000 shown)

Tissue Equivalents	Liver 67400	Adrenal gland 35000	Lungs 31300	Exorbital lacrimal gland 30000	Pituitary gland 29600
	Intra-orbital lacrimal gland 27400				

Metabolism

The metabolism of cobimetinib has been evaluated *in vivo* in dog, rat and human. Studies and results are presented in Table 11.

Table 11: Summary of findings in non-clinical metabolism studies

Study/ Report	Species	Dose, regime	Findings
09-0833	Rat	30 mg/kg, oral, single dose	Plasma; parent 63.3% male/74.1% female, 11 metabolites all below 6.7% Urine; parent 0.3% male/0.7% female, 15 metabolites all below 0.6% (total excretion; <3.3% of dose) Bile; parent <10%, M7 40.2% male/50.6% female Feces; parent 5.6% male/9.1% female. M10; 40.8% male/51.2% female. (total excretion; 85.2% male/84.8 female).
10-0735	Dog	5 mg/kg, oral, single dose	Plasma; parent 65.8% male/64.2 female, !0 metabolites all below 9% Urine; parent 0.3% male, 0.2% female, 9 metabolites all below 1% (total excretion 7% male/6.3% female) Bile; major metabolites; M7, M9, M20, M40 3.4-4.9% of dose Faeces; parent 3.2% male/2.4% female. (total excretion; 81.8% male/83.3% female).
12-3095	Human	20 mg, oral, single dose	Plasma; parent 13.9-32.1%, M16>10%, Urine; parent 1.6%, M14 1.1%, M15 2.1%, (total excretion 17.8%) Faeces; parent 6.6%, M5 5.2%, M29 6.9%, M56 5.3%, (total excretion; 76.5%).

Excretion

Excretion Mass Balance and Pharmacokinetics of Radioactivity Following a Single Oral Dose of [14C]GDC-0973 to Male and Female Sprague Dawley Rats (Study 09-0344)

There were four groups of male and female Sprague Dawley rats. All groups were administered a single oral dose of [14C]GDC-0973. Group 1 consisted of 3 male and 3 female rats, and was used for evaluation of excretion mass balance. Group 2 was comprised of 3 male and 3 female bile duct cannulated (BDC) rats, and was used to characterize the excretion of radioactivity in bile, urine, and faeces. Group 3 consisted of 3 male and 3 female rats in which the pharmacokinetics of plasma total radioactivity was evaluated. The results are presented in Table 12.

Table 12: Summary of recovery of radioactivity following oral administration of [14C]GDC-0973 to group 1 and 2 male and female rats

	% of dose recovered			
	Intact males (0-192h)	Intact females (0-192h)	BDC males (0-48h)	BDC females (0-48h)
Urine	2.2 ± 0.3	3.5 ± 0.5	2.6 ± 0.3	4.4 ± 0.4
Faeces	85.2 ± 1.6	84.8 ± 2.8	8.0 ± 1.3	8.4 ± 0.8
Bile	NS	NS	80.6 ± 2.3	74.4 ± 1.9
Cage Residue	0.5 ± 0.4	1.2 ± 0.6	0.4 ± 0.1	0.9 ± 0.1
Carcass	0.9 ± 0.3	0.6 ± 0.1	ND	5.1 ± 1.4
Total	88.7 ± 2.0	90.0 ± 1.6	91.6 ± 0.9	93.1 ± 1.3

Determination of Radiolabelled Mass Balance, Routes of Excretion, and Metabolic Profiles of [14C]GDC-0973 in Intact and Bile Duct-Cannulated Dogs (Study 09-3129)

Dogs were assigned to two groups for this study. At designated times following dosing, blood, urine, faeces, bile (group 2 only). The findings are presented in Table 13.

Table 13: Summary of recovery of radioactivity following oral administration of [14C]GDC-0973 to dogs

	% of dose recovered		
	Intact males (0-240h)	Intact females (0-240h)	BDC males (0-168h)
Urine	7.02	6.32	6.34
Faeces	81.80	83.30	18.60
Bile	NS	NS	65.00
Cage Residue	1.86	1.43	0.94
Total	90.7	91.05	89.94

2.3.4. Toxicology

Single dose toxicity

The toxicity of single administration and repeat dose administration of cobimetinib was investigated in the rat and dog species. Genotoxicity was investigated using the general battery of tests. Reproductive and developmental toxicity was investigated by oral gavage in rats and in a 28-day juvenile rat study. Local tolerance was investigated in rats and phototoxicity was investigated in vitro using 3T3 mouse fibroblasts and in vivo in a single dose study in rats.

Single dose toxicity

Table 14: Overview of the single-dose toxicity studies with cobimetinib in the rat and the dog

Study ID GLP status	Species/ nr/gender /group	Doses (mg/kg) / Route/ Formulation	Duration of dosing	Major findings	Approx. Lethal Dose (mg/kg) / Observed max non-lethal dose

					(NOAEL)
XL518-NC-002 yes	Rat/Crl:CD(SD) 5F 5M (in each of Groups 1–4 and 8 [toxicity group]) 9/F, 9/M (in each of Groups 5–7 and 9 **[toxicokinetic group**])	0, 30, 75, 150, 300 PO Distilled water	1 day	At doses higher than NOAEL, toxic effects involved hematopoiesis, liver, coagulation, lymphopoiesis, and phosphorus metabolism. **≥ 75 mg/kg: (HED=12.16 mg/kg; 730 mg = 12.2-fold human dose)** -Moribund sacrifice and/or death (day 3) -Hunched posture, abnormal behavior (ataxic and/or hypoactive), recumbency (midline ventral abdomen), nonformed faeces, eye discharge (clear and/or red), squinted eyes, irregular respiration, coloured haircoat (perineal area, midline ventral abdomen, and/or nose), cold to touch, and/or pale body -Slightly to markedly higher neutrophil counts -Slightly higher erythrocyte count, haemoglobin, and haematocrit -Slightly higher prothrombin time and activated partial thromboplastin time values (Day 3) -Lower reticulocyte counts and slightly lower platelet counts (day 3) - High values for ALT, AST, and inorganic phosphorus -Slightly to moderately lower total protein, albumin, and albumin:globulin ratio values -Slightly lower chloride values and slightly higher urea nitrogen concentration **75 & 150 mg/kg & F 300 mg/kg:** -Slightly higher total leukocyte counts **300 mg/kg: (HED=48.65 mg/kg; 2919 mg = 48.6-fold human dose)** -Lysis and depletion of lymphocytes in the thymus -Degeneration of the red pulp of the spleen -Degeneration and necrosis in the bone marrow in the sternum and femur -Coagulative necrosis in the adrenal cortex -Increased apoptosis/necrosis in the ovary -Fibrinous thromboemboli in the choroid plexus of the brain -Increased apoptosis of epithelial cells in the seminal vesicles, epididymis, and vagina **30 mg/kg (HED=4.86 mg/kg; 292 mg = 4.9-fold human dose)**	75 mg/kg 30 mg/kg
XL518-NC-001 No	Dog, Beagle 1F 1M	10, 30, 100 PO Distilled water	Escalating dose on Study Days 1, 3, and 5	**100 mg/kg: (HED=54 mg/kg; 3240 mg = 54-fold human dose)** -Neither dog survived -Emesis and mucoid, discoloured feces -M: laboured respiration, hypoactivity, mucoid feces, and foamy yellow vomitus -M: slight decrease in erythrocyte count, haemoglobin, and haematocrit **30 mg/kg: (HED=16.22 mg/kg; 973 mg = 16-fold human dose)** -Decreased food consumption and emesis -F: mucoid feces -F: slightly higher prothrombin time and activated partial thromboplastin time -F: Higher ALK, slightly increased inorganic phosphorus -Body weight loss in the male (4%) and female (6%) -Lower reticulocyte counts and slightly higher neutrophil -Slight increase in proteinuria **≥ 10 mg/kg: (HED=5.41 mg/kg; 324.6 mg = 5.4-fold human dose)** -Slightly higher aspartate aminotransferase	100 mg/kg 30 mg/kg (MTD between 30 and 100 mg/kg)
XL518-NC-003 Yes	Dog, Beagle 2M, 2F TK	0, 10, 30, 60 PO Distilled water	1 day	At doses higher than NOAEL, toxic effects involved GI and hepatic toxicities besides moribund condition. **60 mg/kg: (HED=32.43 mg/kg; 1945 mg = 32-fold human dose)** -All animals died or were sacrificed by Day 3 **≥ 30 mg/kg : (HED=16.22 mg/kg; 973 mg = 16-fold human dose) :** -Hypoactivity, ocular discharge, tremors, emesis, reduced body temperature, paleness (gums/skin), labored respiration, and	30mg/kg* 10mg/kg

				recumbency in unscheduled deaths - Lower reticulocyte, lymphocyte, and eosinophil counts; increased erythrocyte count, hemoglobin, and hematocrit (Day 3) - Increased prothrombin time and activated partial thromboplastin time (Day 3) - Increased urea nitrogen, creatinine, total protein, globulin, inorganic phosphorus, ALK, AST, and cholesterol; decreased calcium (Day 3) - Low urine specific gravity, high urine volume and urinary protein (Day 3) - Discoloration of small and large intestines (Day 3) - Epithelial degeneration/necrosis in small and large intestines and bone marrow degeneration of the femur and sternum (Day3) **30 mg/kg:** -Both males and one female died* or were sacrificed by Day 3 -F: Weight loss (8%) (Day 4) -F: Notably decreased food consumption (through Day 10) -F: Increased reticulocyte and decreased eosinophil counts (Day 15) **≥ 10 mg/kg: (HED=5.41 mg/kg; 324.6 mg = 5.4-fold human dose)** -Fecal changes (color/liquid/mucoid) -Presence of blood and erythrocytes in the urine	

Repeat dose toxicity

Table 15: Overview of the non-pivotal repeat-dose toxicity studies with cobimetinib in the rat and the dog

Study ID GLP status	Species / nr/gender /group	Doses (mg/kg) / Route/Formulation	Duration of dosing	Major findings	NOEL/ NOAEL (mg/kg /day)
TOX-021406-01-IND No	Rat/Crl: CD(SD) **6F** **TK**	0, 3, 10, 30, 100, 300 PO Water	15 days	Only F Mortality: ≥ 30 mg/kg: all dead Clinical signs: ≥ 3 mg/kg: scratching 10 mg/kg: skin toxicity (ulcerations, surface exudates, acanthosis) ≥ 30 mg/kg: body weight loss (20-25%) ≥ 100 mg/kg: ↓ locomotor activity, diarrhoea Clinical chemistry: 10 mg/kg: ↑ ALT and AST; and ↓ albumin, total protein, Ca^{2+} Haematology: 10 mg/kg: ↑ neutrophils, monocytes, and basophils; ↓ red blood cells, haemoglobin, and haematocrit Microscopic observations: ≥ 30 mg/kg: degenerative changes in bone marrow (erythroid, myeloid, and megakaryocytic depletion, hypocellularity, necrosis, and haemorrhage), small intestine (haemorrhage), and liver (hepatic portal leucocytosis and centrilobular necrosis).	MTD 10mg/kg
XL518-NC-001 No	Dog, Beagle 1M, 1F **TK**	3, 10, and 30 PO Distilled water	7 days	Mortality: all dead (except 1M at 3mg/kg) Clinical signs: 3 mg/kg: macroscopic GI mucosal toxicity, hypoactivity, dehydration, faecal changes (mucoid, discoloured, non-formed, liquid), emesis, ↓ body weight, ↓ food consumption Clinical chemistry: 3 mg/kg: effects on liver and kidney; ↓ Ca^{2+}, ↑ cholesterol and inorganic phosphorus; F: ↓ albumin, ↑ globulin concentration 10 mg/kg: ↓ Ca^{2+}; ↑ ALT, AST, ALK, phosphorus Haematology: 3 mg/kg: effects on lymphoid organs and bone marrow (↓ reticulocyte, ↑ total leukocyte and neutrophil, F: ↓ platelet); coagulopathy (F: ↑ activated partial thromboplastin time) 10 mg/kg: ↓ reticulocyte, lymphocyte, eosinophil; F: ↓ total leukocyte, neutrophil, basophil, M: ↑ leukocyte, neutrophil; F: ↑ activated partial thromboplastin time; ↑ prothrombin time Macroscopic observations: 3 mg/kg: M: brown/tan/pale liver; rough mucosa in the pyloric stomach with white foci and a distended urinary bladder; F: depressed area in the cardiac stomach and red mucosa of the	NOAEL<3

				jejunum and ileum 10 mg/kg: M: linear red discoloration of the jejuna mucosa 30 mg/kg: multifocal to diffuse red discoloration of the gastrointestinal mucosa; F: brown/tan/pale liver	

The repeat-dose toxicity of cobimetinib was evaluated in pivotal studies in Sprague Dawley rats and in Beagle dogs for up to 13 weeks. Major findings as well as the NOAEL values proposed by the applicant are summarized below.

Table 16: Overview of the pivotal repeat-dose toxicity studies with cobimetinib

Study ID GLP status	Species / nr/gender /group	Doses (mg/kg) / Route/Formulation	Duration of dosing	Major findings	NOAEL (mg/kg/day)
XL518-NC-004 Yes	Rat/Crl: CD(SD) 10F, 10M **Recovery: 5F, 5M** **TK** 10F, 10M day 1, day 28 (except F at 10 mg/kg: day 1, day 15)	0, 1 , 3, 10 PO Distilled water 0, 10 1 , 3, 10	4 weeks 28d post-dose	Mortality: 10 mg/kg: 3 F by **day 15 (dosing terminated for all F; 5 to recovery; 7 euthanized**); 3M by day 26 1 & 3 mg/kg: no unscheduled deaths Clinical signs: 10 mg/kg: **severe clinical signs in F** and less severe in M; declining condition (hunched, hypoactive, rough haircoat), ↓ body weight and food consumption in F; skin lesions (sore/scabs) 3 mg/kg: ↓ food consumption in F Clinical chemistry: 10 mg/kg: parameters more pronounced in F. ↑ BUN, AST, ALT, globulin in M&F; ↑ ALK, GGT, phosphorus in F; ↓ albumin and A/G ratio in M&F 3 mg/kg: ↑ AST in M; ↑ ALT Hematology: 10 mg/kg: ↓ RBC, HGB, HCT values; ↑ reticulocyte in F, ↑ neutrophil in F & M and ↑ WBC, monocyte, and large unstained cell counts in F; ↓ mean corpuscular haemoglobin concentration. ↓ lymphocyte and eosinophil; ↓ platelet Macroscopic observations: 10 mg/kg: dose-dependent ↑ spleen, ↓ thymus, liver and ovary weight in F; skin abrasion in F **1 & 3 mg/kg: dose-dependent ↓ spleen!, ↓ thymus, liver and ovary weight in F** Microscopic observations: 10 mg/kg: histopathologic **liver** tissue damage correlated with changes in ALT, AST, ALP and GGT; **thymic** necrosis/depletion; **ovarian** apoptosis/necrosis and follicular cysts. All correlated w/ macroscopic changes. Damage in spleen, mesenteric and mandibular lymph nodes, GI tract, kidney, skin/subcutis, heart, ovary, and vagina. **≥ 3 mg/kg: low incidence degenerative findings in adrenal cortex, thymus and bone marrow.** **Reversibility**: **All microscopic findings reversed except mandibular lymph node damage**. Haematology and clinical chemistry reversible; body weights decreased; skin sore/scab; higher mean corpuscular volume and mean corpuscular haemoglobin values in F **TK:** ↑ dose-dependent exposure in F compared to M (study report TK in absorption PK section: similar exposure except for 10 mg/kg at day 16 in F)	1 mg/kg
XL518-NC-012 Yes	Rat/Crl: CD(SD) 10F, 10M **Recovery: 5F, 5M**	0, 0.3, 1.0, 3.0 PO Distilled water 0, 3.0	13 weeks 29d post-dose	No mortality. (1F dead at 3 mg/kg due to procedure) No cobimetinib-related adverse findings. (sensitivity to touch was observed but not considered adverse) **Reversibility**: Unremarkable clinical signs **TK:** ↑ dose-dependent exposure in F compared to M for cobimetinib and metabolite EXEL0382 (gender-effect). EXEL0382 first detected at 1 mg/kg in F only, then in both M&F at 3 mg/ kg	3.0 mg/kg

	TK 12F, 12M day 1, day 45, day 90				
XL518-NC-005 Yes	Dog, Beagle 3F, 3M TK **Recovery: 2F, 2M**	0, 0.1, 0.3, 1.0 PO Distilled water 0.1, 1.0	4 weeks 28d post-dose	No cobimetinib-related mortality. No cobimetinib-related adverse findings. **Reversibility**: no delayed effects **TK**: systemic exposure increased slightly greater than dose-proportionally with increasing dose; but no meaningful drug accumulation with repeating dosing than on day 1. No gender-associated differences in exposure. T1/2=4.8-7.5hrs	1.0 mg/kg
XL518-NC-013 Yes	Dog, Beagle 5F, 5M **Recovery: 2F, 2M** TK	0, 0.3, 1.0, 3.0/1.0 PO Distilled water 0.3, 3.0/1.0	13 weeks 28d post-dose	Mortality: 3 mg/kg: not tolerated at day 10, drug holiday day 11-21 then 1 mg/kg; death due to gastroenteropathy (1F, 2M) 1 mg/kg: death (1F) Clinical chemistry: 3 mg/kg: ↓ total protein and albumin (d11) Hematology: 3 mg/kg: ↓ RBC mass, absolute reticulocyte and eosinophil (d11) Microscopic observations: 3/1 mg/kg & 1 mg/kg: oesophageal mucosal epithelial degeneration and inflammation (drug-related only in M) **Reversibility**: yes **TK**: **Cobimetinib**: $T_{1/2}$=4.96-7.33hrs appears consistent across the dose levels and throughout 90 days of dosing. Low to moderate accumulation on days 30, 59, and 90 for 0.3 and 1 mg/kg (high accumulation on day 10 at 3 mg/kg). No marked gender effect. **EXEL0382**: Low dose-dependent exposure relative to cobimetinib exposure. No gender effect.	0.3 mg/kg

Abbreviations:
F: female, M: male
ALK: alkaline phosphatase, ALT: alanine aminotransferase , AST: aspartate aminotransferase, RBC: red blood cell, HGB: haemoglobin, HCT: haematocrit, BUN: blood urea nitogren, A/G: albumin to globulin, GGT: gamma glutamyl transferase, BBLQ: below the lower limit of quantitation

Genotoxicity

The results of the in vitro studies on genotoxicity are presented in Table 17.

Table 17: Genotoxicity studies with cobimetinib

Type of test / study ID / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results Positive / negative / equivocal
Gene mutations in bacteria, XL518-NC-008, GLP	*Salmonella typhimurium*; TA98, TA100, TA1535, TA1537. *Escherichia coli*; WP2 uvrA	10-3000 ug/plate, +/- rat S9	Non-mutagenic
Chromosomal aberrations in mammalian cells, X518-NC-007, GLP	Primary human lymphocytes	30-120 ug/ml, +/- rat S9	non-clastogenic
Micronucleusn in vivo, 13-1420, GLP	Rat, micronuclei in bone marrow	3-60 mg/kg	negative for micronucleus formation

Carcinogenicity

The applicant did not submit studies on carcinogenicity (see non-clinical discussion).

Reproduction Toxicity

Fertility and early embryonic development

The data show that cobimetinib induces degenerative changes in the reproductive organs on rats and dogs. In single-dose toxicity studies, increased apoptosis/necrosis was present in rats (300 mg/kg: corpora lutea and seminal vesicle, epididymal, and vaginal epithelial cells) and dogs (30 and 60 mg/kg: epididymal epithelial cells) euthanized in moribund condition on Days 2 and 3. In repeat-dose studies, increased corporeal apoptosis/necrosis and mineralization of the corpora lutea and larger follicular cysts were present in rats at the non-tolerated 10-mg/kg/day dose. The findings were present at non-tolerated dose levels (300 mg/kg in rat, 30/60 mg/kg in dog and ≥10 mg/kg/day in rat). The findings in rats dosed 10 mg/kg/day (0.7 times clinical exposure) were fully recovered after 28 days.

Embryofoetal development

Pregnant female rats (10 animals/group) were administered daily oral doses of 0.3, 1, 3, and 10 mg/kg cobimetinib or vehicle alone on day of gestation (DG) 7 through 17. The findings of the study are presented in Table 18.

Table 18: Summary of the embryo-foetal developmental study of cobimetinib administered in rats

Study ID	Species Strain Nr/sex/group	Dose (mg/kg/day) Route	Duration	Cmax,ss [nM]b	AUC0-24h,ss [nM•h]b	Major Findings	NOAEL (mg/kg/day)
Embryo-foetal development							
13 0026 GLP	Crl:CD(SD) rat 10	0 0.3	10 days DG 7-17			F0: 10 mg/kg: 1D euthanized for declining condition, ↓ body weight gain and food consumption	
	daily	1				1-3 mg/kg: minor ↓ in weight gain and food consumption; well tolerated	
	po	**3**		**57.4 ng/ml**	**662 ng▪ hr/ml**	All doses: no gross lesions	**3 [fetal= maternal]**
		10				F1: 10 mg/kg: **Embryolethality** - in D with highest ↓ in weight gain (may be secondary to maternal toxicity). **Fetal malformations** of the great vessels and skull (small eye sockets), fused ribs - in D without marked ↓ weight gain (direct effect on fetus). 1-3 mg/kg: no effects on litter parameters	
	TK:					TK: maternal plasma exposures generally dose dependent (AUC & Cmax dose proportional (0.3-3 mg/kg) and greater than dose proportional (3-10 mg/kg).	

The applicant did not submit studies in animals to evaluate the potential effects of cobimetinib on pre/post-natal development (see non-clinical discussion).

Studies in which the offspring (juvenile animals) are evaluated were performed. The study was to evaluate the potential toxicity and determine the toxicokinetic profile of cobimetinib on juvenile rats when administered once daily via oral gavage beginning on Postnatal Day 10 (PND10 or Study Day 1) and continuing for 28 days.

Table 19: Summary of the embryo-foetal developmental study of cobimetinib administered in rats - Study 13-0578

Study ID	Species Strain Nr/sex /group	Dose (mg/kg/ day) Route	Duration	Cmax, ss [nM]b	AUC0-24h,ss [nM•h]b	Major Findings	NOAEL (mg/kg /day)
Juvenile toxicity							
13 0578 GLP	Rat/Crl: CD(SD) 10F 10M	0, 0.3, 1, 3 po PND10	28 days Necropsy day 39	4.95 ng/ml	F: 63.7 ng • hr/mL M: 60.6 ng • hr/mL	**Toxicity evaluation phase:** Mortality: 3mg/kg: death (1M, 1F PND17) with no gross or microscopic lesions Hematology: 3 mg/kg: ↓ circulating lymphocytes 1-3 mg/kg: ↑ red cell mass, Clinical Chemistry: 3 mg/kg: ↓ hepatocellular glycogen 0.3-3 mg/kg: ↑ phosphorus 1-3 mg/kg: ↑ total bilirubin, ↓ tryglycerides Macroscopic observations: 1-3mg/kg: ↓ thymic, liver, weights 3 mg/kg: ↓ spleen weight ≥ 0.3 mg/kg: ↓ thyroid/parathyroid weights Microscopic observations: 3mg/kg: ↑ single-cell necrosis in thymic lymphocytes	1
TK	6F, 6M 30F 30M	0 0.3, 1, 3, 10				**TK phase:** Mortality: 10mg/kg: death (10M, 7F at PND13) ≥ 3mg/kg: dose well tolerated TK: Plasma exposures generally ↑ with dose level and ↑ in F at the 0.3, 1, and 3 mg/kg but not at 10 mg/kg on Day 1. Exposures were higher on Day 1 than Day 28 in both male and female rats. By Study Day 28, exposures were similar between M & F.	

Toxicokinetic data

Table 20: Summary of the toxicokinetic data

Species/Study/ Duration	Dose (mg/kg/day)	Sex	C_{max} (ng/ml)		AUC (ng*h/ml)	
			End of study	Animal to human ratio[a]	End of study	Animal to human ratio[a]
Patients/NO25395	60 mg	M/F	273	-	4340	
Rat, XL518-NC-006, Single dose	30	M	583	2.1	6090	1.4
Rat, XL518-NC-009, Single dose	30 100 300	M	430 1910 2810	1.6 7 10.3	NC	NC
Dog, XL518-NC-010, Single dose	0.3 1 3	M	16.2 60.2 233	0.06 0.2 0.9	NC	NC
Rat, XL518-NC-002,	30	F	620	2.2	8340	1.9

Single dose		M	384	1.4	5220	1.2
	75	F	1140	4.1	20300	4.7
		M	1060	3.9	15400	3.5
	150	F	3480	12.7	25900	5.9
		M	3670	13.4	21000	4.8
	300	F	8330	30.5	72600	16.7
		M	6100	22.3	38100	8.8
Dog, XL518-NC-003, Single dose	10	F	1870	6.8	29400	6.8
		M	1660	6.1	24200	5.6
	30	F	4690	17.2	84400	19.4
		M	8400	30.1	97800	22.5
	60	F	11500	42.1	140000	32.3
		M	8760	32.0	127000	29.3
Rat, XL518-NC-004, Repeat dose	1	F	12.7	0.05	157	0.04
		M	10.3	0.04	102	0.02
	3	F	55.4	0.2	602	0.1
		M	28.6	0.1	330	0.08
	10	F	ND	ND	ND	ND
		M	357	1.3	2892	0.7
Rat, XL518-NC-012, Repeat dose	0.3	F	4.48	0.01	47.4	0.01
		M	2.19	0.008	28.1	0.006
	1	F	17.8	0.06	176	0.04
		M	9.57	0.03	114	0.02
	3	F	77.4	0.3	772	0.2
		M	41.4	0.15	460	0.1
Dog, XL518-NC-001, Repeat dose	0.1	F	11.7	0.04	107	0.02
		M	15.9	0.06	104	0.02
	0.3	F	49.4	0.2	556	0.1
		M	34.2	0.1	335	0.08
	1.0	F	263	0.9	2420	0.6
		M	343	1.2	4060	0.9
Dog, XL518-NC-005, Repeat dose	0.1	F	15.9	0.06	104	0.02
		M	11.7	0.04	107	0.02
	0.3	F	34.2	0.1	335	0.08
		M	49.4	0.2	556	0.1
	1.0	F	343	1.2	4060	0.9
		M	263	1.0	2420	0.6
Dog, XL518-NC-013, Repeat dose	0.3	F	30.5	0.1	330	0.08
		M	46.4	0.2	480	0.1
	1	F	204	0.7	2110	0.5
		M	195	0.7	2460	0.6
	3*	F	892	3.2	10400	2.3
		M	2310	8.4	19300	4.4
Rat, 13-0026, Embryo-foetal toxicity	0.3	F	4.29	0.01	69.3	0.01
	1		19.8	0.07	299	0.07
	3		57.4	0.2	662	0.2
	10		388	1.4	6020	1.4
Rat, 13-0578, Juvenile toxicity	0.3	F	20.5	0.08	89.2	0.03
		M	1.92	0.007	34.3	0.008
	1	F	27.0	0.01	438	0.1
		M	26.1	0.09	371	0.09
	3	F	142	0.5	2240	0.5
		M	29.3	0.1	585	0.1
	10	F	284	1	3900	0.9
		M	329	1.2	4680	1.1
Rat, 10-1473, Local tolerance	1	M	105	0.4	301	0.07
	3		311	1.1	994	0.2
Rat, 13-2485, Phototoxicity	5	F	74.9	0.3	1180	0.3
	15		388	1.4	5970	1.4
	60		1990	7.3	31200	7.2

*data at day 10

Local Tolerance

Local tolerance of cobimetinib was assessed in a single-dose intravenous study (0, 1, 3 mg/kg) in rats Crl:CD(SD) (6M /group) with a 13-day recovery period to support IV dose administration (study 10-

1473). There were no signs of local dermal irritation (macroscopic or microscopic) at the injection site following administration of the vehicle or cobimetinib.

Other toxicity studies

In vitro phototoxicity studies

Cobimetinib absorbed UV light significantly between 300 and 400 nm. Therefore, cobimetinib was assessed for possible phototoxic potential in vitro by the 3T3 mouse fibroblast neutral red uptake assay and in vivo by a phototoxicity study in pigmented rats.

Table 21: Summary of phototoxicity studies

Study ID	Species Strain / Nr/sex/ group	Dose	Duration	Major Findings
In vitro Phototoxicity evaluation				
13-1490 GLP	Fibroblasts/Mouse/ Balb/c 3T3	0.032, 0.100, 0.316, 1.00, 3.16, 10.0, 31.6, 100 mg/L	2 hours	Phototoxic potential (photoirritancy factor=2.2) IC50=64 ug/ml non-irradiated cells IC50=30 ug/ml UV-irradiated cells
In vivo Phototoxicity evaluation				
13-2485 GLP	Rat (Long Evans) 5F	0, 5, 15, 60 mg/kg single po dose +UV irradiation 60 mg/kg -UV irradiation	42 minutes about 4hr after dosing (to reach Cmax)	No cutaneous or ocular phototoxicity.
TK	3F 6F	0 5, 15, 60 mg/kg		

Impurities

The batches used during pivotal non-clinical toxicity studies show a high degree of purity and no impurity were above the 0.15% qualification level.

2.3.5. Ecotoxicity / environmental risk assessment

Table 22: Summary of main study results

Substance (INN / Invented Name): Cobimetinib					
CAS-number (if available): 1369665-02-0 (hemifumarate), 934660-93-2 (free base)					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	Log Dow = 1,19 at pH 5 Log Dow = 1,19 at pH 7 Log D0w = 2,33 at pH 9			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	< 4,5			not B
	BCF	not performed			B/not B
Persistence	DT50 or ready biodegradability	$DT_{50,\ water}$ = 3,4-4,8 $DT_{50,\ whole\ system}$ = 211 - > 1000			vP
Toxicity	NOEC or CMR	R?			potentially T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{\ surfacewater}$, default or refined (e.g. prevalence, literature)	0,300	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc,\ ads}$ =2977,1 l/kg (soil) $K_{oc,\ ads}$ =2877,3 l/kg (soil) $K_{oc,\ ads}$ =3016,5 l/kg (soil) $K_{oc,\ ads}$ =2356,1 l/kg (soil) $K_{oc,\ ads}$ =4901,9 l/kg (sludge) $K_{oc,\ ads,\ all}$ =3225,9 l/kg			Terrestrial assessment not triggered
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 3,4-4,8 $DT_{50,\ whole\ system}$ = 211 - > 1000 80 % shifting to sediment			vP Sediment assessment triggered
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	ErC_{50} EyC_{50} ErC_{10} EyC_{10}	11,8 2,25 0.989 0,265	mg/L	*Desmodesmus subspicatus*
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.0898	µg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	0,109	mg/L	*Danio rerio*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50} EC_{20}	> 1000 102,7	mg/L	
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	79,1	mg/k	*Chironomus*

				g	*riparius*

Based on the data provided by the applicant for phase I and II studies, cobimetinib is not a PBT substance.

2.3.6. Discussion on non-clinical aspects

Cobimetinib has demonstrated selectivity for MEK1/2 in *in vitro* and *in vivo* models. Cobimetinib inhibited the phosphorylation of ERK1/2 and the proliferation and induction of apoptosis in BRAF-mutant melanoma cell lines. This was also shown in cell lines with acquired resistance to vemurafenib. Therefore, the combination of vemurafenib and cobimetinib appears to have a more profound effect on inhibiting the MAPK pathway and tumour growth in vivo than either compound alone.

Pharmacology and toxicology studies were carried out with cobimetinib HCL or hemifumarate salts by the oral route of administration as this is the proposed therapeutic route in humans. The animal species and strains used in these investigations are considered adequate based on the similarities in the pharmacokinetic and metabolic handling of cobimetinib between the selected species and human.

Cobimetinib was characterized by low to moderate CL and moderate to high volumes of distribution in animals. Cobimetinib was well absorbed in rat and dog. Of the cobimetinib-related radioactivity in plasma of rat and dog the major circulating exposure was from unchanged cobimetinib. The metabolism of cobimetinib was extensive with less than 10% of the dose excreted as unchanged cobimetinib in urine, feces, or bile. Biliary excretion of cobimetinib-related metabolites into feces was the major pathway for cobimetinib elimination.

In both rat and dog cobimetinib induced death a mid- and high doses. Major clinical target organs were hematopoiesis, liver, skin, GI, coagulation, lymphopoiesis and phosphorus metabolism. Microscopic degenerative, necrotic, and/or apoptotic changes were found in high dose animals in the liver, kidney, gastrointestinal tract tissues, bone marrow, lymphoid tissues, reproductive tract tissues (ovary, seminal vesicles, epididymis, and vagina), and adrenal cortex. The nonclinical toxicology findings associated with cobimetinib administration to rats and dogs were consistent with pharmacologically mediated changes as a result of MEK1/MEK2 inhibition and disruption of MAPK signalling pathways. Toxicity in the GI tract lead to decreased food consumption and body weight, emesis, mucoid discoloured faeces and hypoactivity. Thus, diarrhoea has been included as an important identified risk in the RMP and will be managed through routine pharmacovigilance. The toxicokinetic data from the pivotal repeat-dose toxicity studies were performed under sub-clinical exposure in animals dosed for the full length of the study in order to be able to acquire safety for the required 4-week and 13-week studies. This is considered acceptable considering the high toxicity and mortality rate observed at clinical exposure although very little information on the toxicity of cobimetinib after long-term treatment can be derived from these studies. As a consequence, the NOEAL in the pivotal toxicity studies at sub-clinical exposures were 0.05/0.15 times the clinical exposure in the rat 4 week and 13 week studies, respectively. In dog the same exposures were 1/0.1 times the clinical exposure in the 4 week and 13 week studies, respectively.

Toxicity studies in rats and dogs identified generally reversible degenerative changes in the bone marrow, gastrointestinal tract, skin, thymus, adrenal gland, liver, spleen, lymph node, kidney, heart, ovary, and vagina at plasma exposures below clinical efficacious levels. Dose limiting toxicities included skin ulcerations, surface exudates, and acanthosis in the rat and chronic active inflammation and degeneration of the oesophagus associated with varying degrees of gastroenteropathy in dogs (SmPC section 5.3).

In a repeat dose toxicity study in juvenile rats, cobimetinib systemic exposures were 2 to 11 fold higher on post-natal day 10 than on post-natal day 38 when exposures were similar to those in adult rats. In juvenile rats, cobimetinib administration resulted in similar changes as seen in the pivotal toxicity studies in adults, including reversible degenerative changes in the thymus and liver, decreased spleen and thyroid/parathyroid weights, increased phosphorus, bilirubin and red cell mass and decreased triglycerides. Mortality occurred in juvenile animals at a dose (3 mg/kg) which did not lead to mortalities in adult animals (SmPC section 5.3)

Based on the i*n vitro* data hERG assay, cobimetinib appeared to increase the potency of vemurafenib. However, the *in vivo* ECG study in dogs with cobimetinib did not show any effect. It is noteworthy that the study was undertaken at lower than clinical exposures and is therefore of limited value. Cardiovascular safety of cobimetinib in combination with vemurafenib has not been evaluated *in vivo*. *In vitro*, cobimetinib produced moderate hERG ion channel inhibition (IC_{50}= 0.5 µM [266 ng/mL]), which is approximately 18 fold higher than peak plasma concentrations (C_{max}) at the 60 mg to be marketed dose (unbound C_{max}=14 ng/mL [0.03 µM]) (SmPC section 5.3).

Cobimetinib was found to be non-mutagenic when tested in bacterial cell (Ames) assay, human lymphoma assay or rat micronucleus test. The lack of dedicated carcinogenicity studies is acceptable in accordance with the ICH S9 guide line. Carcinogenicity studies have not been conducted with cobimetinib. Standard genotoxicity studies with cobimetinib were negative (SmPC section 5.3).

The applicant did not submit dedicated fertility and early embryonic development studies. This is acceptable in accordance with the ICH S9 guideline. No dedicated fertility studies in animals have been performed with cobimetinib. In the repeat-dose toxicology studies, degenerative changes were observed in reproductive tissues including increased apoptosis/necrosis of corpora lutea and seminal vesicle, epididymal and vaginal epithelial cells in rats, and epididymal epithelial cells in dogs. The clinical relevance of this is unknown (SmPC section 5.3). The findings were present in rat at sub-clinical exposure levels (0.7 times clinical exposure). The findings were reversible after recovery. Thus, impaired female fertility has been included in the RMP as an important identified risk and will be managed through routine pharmacovigilance (SmPC section 4.6 and 5.3). Reproduction toxicity was evaluated in a study in rat in the high dose group (10 mg/kg/day) dams which showed severe clinical conditions in terms of body weight gain and food consumption. Foetuses from these dams also showed malformations of the great vessels and skull. The high dose was equivalent to a 1.4-times the clinical exposure. Thus, it can be concluded that cobimetinib is teratogenic at clinically relevant levels. When administered to pregnant rats, cobimetinib caused embryolethality and foetal malformations of the great vessels and skull at systemic exposures similar to human exposure at recommended dose (SmPC section 5.3). Therefore, the risk of teratogenicity and developmental toxicity has been included as an important potential risk in the RMP.

Cobimetinib did not induce local toxicity at the injection site in the rat study. However, clinical data show that many patients experience skin toxicities, especially phototoxicity. Cobimetinib treated UV-exposed rats did not show signs of increased skin/eye toxicity compared to vehicle treated animals. The exposures in the high dose group were about 7 times the clinical exposure. Nevertheless, although no evidence was observed in the non-clinical studies, based on clinical safety data photosensitivity was included as an important identified risk (SmPC section 4.2 and 4.8).

The batches used during pivotal non-clinical toxicity studies show a high degree of purity and no impurity were above the 0.15% qualification level. All specified impurities are set below the 0.15% qualification level.

Cobimetinib is not a PBT substance and is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical studies submitted for the marketing authorisation application for cobimetinib in combination with vemurafenib were considered adequate and acceptable for the assessment of the non-clinical aspects. Cobimetinib is considered to have teratogenic potential with developmental toxicity for the foetus. This potential risk is being managed through routine pharmacovigilance.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 23: Clinical efficacy studies

Clinical Study	n Countries	Design	Patient Population	Regimen	Objectives	Status / CSR available
Clinical studies of cobimetinib in cancer patients						
NO25395* (BRIM7) (Phase Ib)	131[a] US, Australia	Multicenter, non-randomized, open-label, dose-escalation study	Patients with locally advanced/ unresectable or metastatic BRAF V600E-mutant-positive melanoma: (i) BRAF inhibitor (BRAFi)-naïve patients: previously treated (but without prior exposure to BRAF or MEK inhibitor therapy) or previously untreated for locally advanced/unresectable or metastatic melanoma (n=63) or (ii) BRAFi progressor patients: progressed after treatment with vemurafenib (n=66)	Stage I: cobimetinib 60, 80, 100 mg QD on 14/14 day schedule and vemurafenib 720, 960 mg BID Stage II: cobimetinib 60 mg QD on 21/7 and 28/0 day schedule and vemurafenib 720, 960 mg BID	Stage I, II: To evaluate the safety, tolerability, pharmacokinetics and efficacy of the vemurafenib and cobimetinib combination	Ongoing / Yes
GO28141/coBRIM* (Phase III)	495 Austria, Belgium, Czech Rep, France, Hungary, Germany, Italy, Sweden, Netherlands, Norway, Spain, UK, Canada, Russia, Australia, Turkey, New Zealand, Switzerland, Israel, USA.	Randomized double blind, placebo-controlled	Patients with BRAF V600-mutated advanced melanoma who have received no prior systemic therapy for their disease.	Cobimetinib 60 21/7 + vemurafenib 960 or placebo BID	To evaluate investigator-assessed PFS (primary efficacy), OS, ORR, DOR, IRF-assessed PFS (secondary efficacy), safety, PK, patient-reported outcome	Ongoing / CSR available in November 2014. Topline results report for primary data cut provided with this MAA

[a] Two vemurafenib-PD patients received cobimetinib monotherapy 60 mg QD on a 21/7 schedule

2.4.2. Pharmacokinetics

Clinical PK data are provided based on eight studies (Table 24). Single doses of cobimetinib have been given to healthy subjects (HV) and patients (Pats) at doses up to 20 mg orally and 2 mg IV.

Table 24: Overview of studies with cobimetinib included in the clinical pharmacology package

Description	Phase	Subject	Formulation	Dose	Reference
MTD - Stage 1, 3w - Stage 1A, 2w - Stage 2, 3w - Stage 2A, 2w - Stage 3 DDI CYP3A, CYP2D6	1	Pats	 Solution (PiB) Capsule (PiC) Capsule Capsule Capsule Capsule	 0.05, 0.1, 0.2 mg /kg 10, 20, 40, 60, 80 mg 60, 80, 100, 125 mg 60 mg 100 mg 60 mg	MEK4592
Absolute F	1	HV	Capsule 5 mg Solution 0.04 mg/ml	20 mg po 2 mg iv	MEK4952
- Relative F, - Food interaction	1	HV	Capsule 5 mg Prototype Tablet 20 mg	20 mg po	MEK4953
Relative F	1	HV	PiC 5 mg Commercial tablet 20 mg		GP28370
Mass balance	1	HV	Solution	20 mg (200 µCi)	GP28369
DDI PPI	1	HV	Prototype tablet 20 mg	20 mg	MEK4954
DDI CYP3A	1	HV	Capsule	10 mg	GP28620
DDI vemurafenib	1b	Pats	Capsule	60, 80, 100 mg	NO25395
Pop PK	–	–	-	Based on study MEK4592 and NO25395	14-1643
PBPK analysis	–	–	-	Based on study 10-0264, MEK4952, GP28369, GP28620	14-1645
Hepatic impairment	1	HV	capsule	10 mg	GP29342 ongoing
Phase III	3	Pats	Final tablet	60 mg	GO28141 ongoing

Absorption

Cobimetinib is characterised as highly soluble and moderate to highly permeable compound and is a Pgp, but not a BCRP, substrate. The estimated fraction absorbed is 88% while the absolute bioavailability is calculated to be approximately 46% indicating extensive first pass metabolism. A high fat meal did not influence the systemic exposure compared to fasted condition. Results are shown in Table 25.

Table 25: Geometric mean (%CV) PK parameters of cobimetinib following a 30-min iv infusion of 2 mg and 20 mg administered orally - Study MEK4952

	IV 2 mg	Oral 20 mg
C_{max} (ng/ml)	21 (36)	15 (26)
t_{max} (h)	–	4 (2, 8)[a]
$AUC_{0-\infty}$ (ng/ml.h)	188 (16)	784 (30)
MAT (h)	–	3 (58)
F (%)	–	46 (25)
CL (L/h)	11[b] (16)	–
V_{ss} (L)	1052 (28)	–
$t_{1/2}$ (h)	74 (17)	66 (18)
Urine excretion (% of dose)	4 (22)	2 (34)
CL_R (L/h)	0.4[c] (20)	0.5[d] (22)

[a] Median (min, max) [b] 178 ml/min [c] 7 ml/min [d] 8 ml/min

The commercial formulation has not been used in the food and DDI studies. Comparable exposure was seen between the formulation used in the studies between the prototype tablet and the capsule (AUC ratio 105 [90%CI 93-118]) and between the commercial tablet and the capsule (AUC ratio 101 [90%CI 94-107]). The commercial tablet was used in the pivotal phase 3 study.

The maximum plasma concentration of cobimetinib, following oral treatment in patients, was reached at median a t_{max} of 2h (range 1-24h), as shown in Table 26.

Table 26: Geometric mean (%CV) PK parameters of cobimetinib following oral dosing with a 20 mg commercial tablet (A) and with20 mg as 4x5-mg capsules (B) under fasted condition

	20 mg commercial tablet	20 mg, 4 x 5-mg capsules
C_{max} (ng/ml)	18 (39)	15 (48)
$AUC_{0-\infty}$ (ng/ml.h)	784 (41)	707 (38)
t_{max}[a] (h)	2 (1, 8)	4 (2, 8)
$t_{1/2}$ (h)	57 (24)	58 (24)

[a] Median (min, max)

Distribution

The *in vitro* protein binding of cobimetinib was determined by equilibrium dialysis at 1-10 µM (about 500 – 5500 ng/ml). The mean unbound fraction (f_u) was calculated to be 5.8% and was independent of the plasma concentration of cobimetinib. The mean fraction cobimetinib bound (f_b) to isolated human serum albumin (HSA; 40 mg/ml) and α1-acid glycoprotein (AAG ; 1 mg/ml) was 57.1% and 95.4%, respectively, at all concentration tested 1-10 µM.

The *in vitro* partitioning of cobimetinib between human blood and plasma was independent of concentration, in the concentration range tested 1-10 µM, and was determined to approximately 1 (0.93-1.05).

The V_{ss} was calculated to 1050 L following an iv dose of 2mg in the study determining the absolute F of cobimetinib.

Elimination

Cobimetinib has a long half-life, mean of 43.6 h with individual half-lives ranging between 23-70h. Once daily dosing resulted in an accumulation of about 2-3 times higher exposure at steady state compared to after a single dose.

The total plasma CL was calculated to 178 ml/min and CL_R to 7 ml/min.

The terminal $t_{1/2}$ of cobimetinib was calculated to about 60-70h in the bioavailability studies in healthy subjects. A shorter $t_{1/2}$ was determined in patients, approx 50h. Once daily dosing, as proposed the dosing regimen, resulted in an accumulation of about 2-3 times higher exposure at steady state compared after a single dose. The total plasma CL was calculated to be 178 ml/min and the CL_R to 7 ml/min (Study MEK4952). Results are reported in Table 27.

Table 27: Exposure (geomean(SD)) of cobimetinib on day 1 and at steady state following once daily dosing for 3w (stage I and II) or 2w (stage IA and IIA) of each 4w-cycle

Dose (mg)	Stage	n[a]	AUC_{0-24h} (ng/ml.h)		C_{max} (ng/ml)		t_{max} (h)		$t_{1/2}$[e] (h)
			Day 1	Steady state	Day 1	Steady state	Day 1	Steady state	
3.2(0.9)[b] (0.05 mg/kg)	I	4 / 3	56(65)	164(160)	4.5(5.8)	11(10)	2 (2-8)	4 (2-4)	80
7.9(2.0)[b] (0.1 mg/kg)	I	2 / 3	68(47)	244(200)	6.9(3.8)	16(15)	1 (1-2)	1 (1-2)	62 (52-73)
13.4(2.4)[b] (0.2 mg/kg)	I	3 / 2	203(130)	387(200)	18(13)	28(9)	1.5 (1-1.5)	2.25 (1.5-3)	48 (47-49)
10	I	3 / 3	242(64)	752(170)	19(5)	53(5)	3 (1-4)	4 (3-4)	53 (34-68)
20	I	5 / 1	440(870)	886	31(69)	57	4 (2-4)	3	51
40	I	6 / 5	785(560)	3840(4600)	72(57)	272(240)	2.5 (1.5-6)	2(1.5-3)	44 (34-62)
60	I	7 / 4	1620(830)	5600(3540)	163(79)	364(210)	2 (1-4)	3 (1.5-4)	44 (23-61)
60	IA	3 / 3	1170(1200)	2670(1750)	78(88)	163(101)	3 (1.5-4)	2 (1.5-4)	59
60	II	19 / 15	2400(2100)	5090(3130)[b]	184(160)	315(220)	3 (1-6)	3 (1-6)	
80	I	7 / 6	3060(950)	8060(10500)	261(110)	525(210)	2 (1.5-2)	2.5 (2-4)	49 (34-65)
80	IA	3 / 3	2130(70)	6020(3830)	167(63)	470(175)	4 (2-24)	2 (2-6)	44

100	IA	8 / 5	3670(2000)	7270(10500)	258(140)	470(511)	3.5 (1.5-6)	3 (1.5-4)	56 (48-71)
100	IIA	21 / 13	3660(2300)	10200(5630)[d]	255(200)	566(300)	3 (1.5-6)	4 (1.5-6)	53 (45-68)
125	IA	6 /3	6330(3600)	19700(11300)	444(350)	1070(540)	2.5 (2-4)	6 (2-6)	48

[a] Day 1 / Steady state [b] mean (SD) [c] Day 14 (stage 2A) [d] Day 21 (stage 2) [e] at steady state

Metabolism

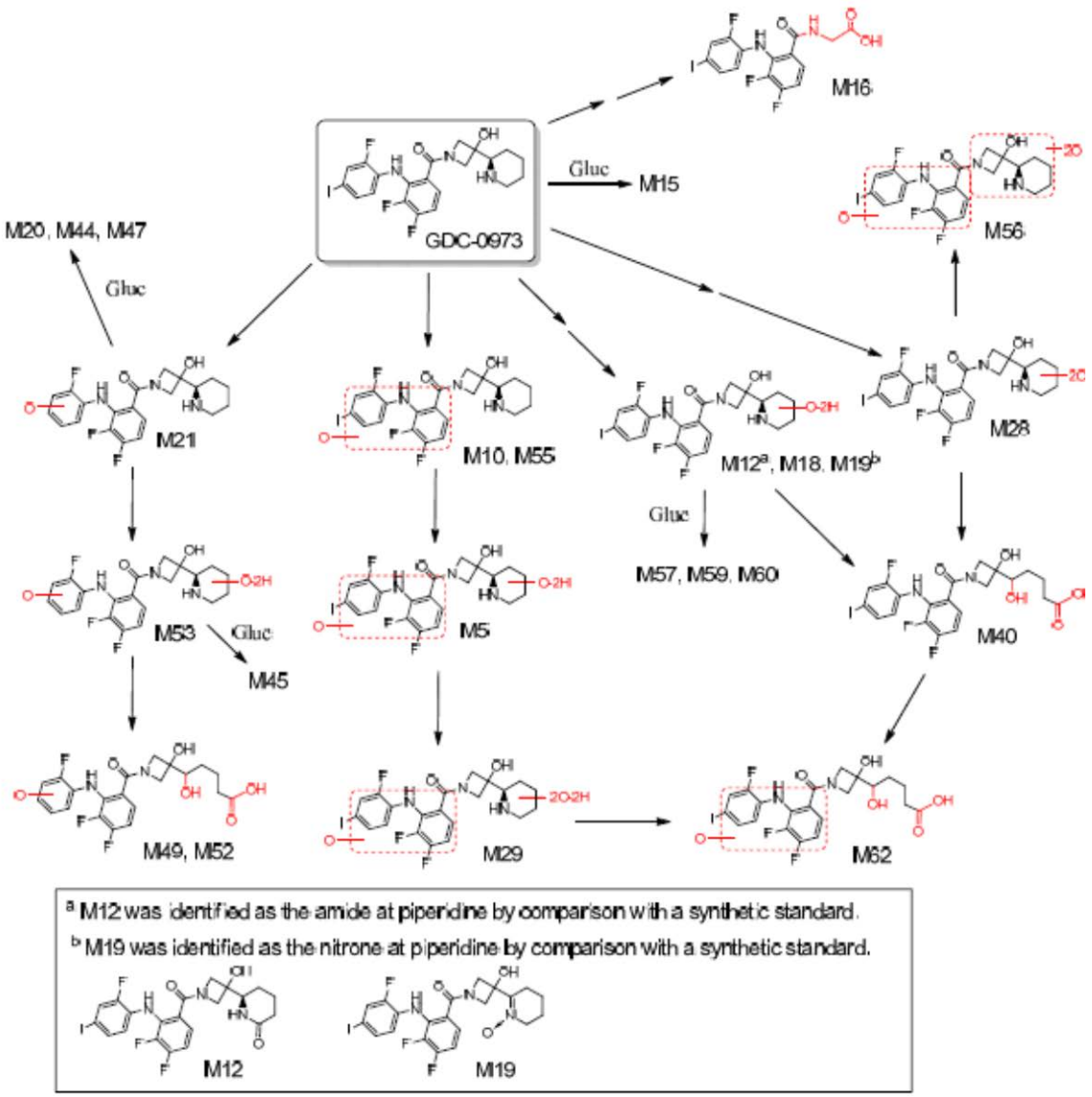
The metabolism of cobimetinib by human liver microsomes (HLM) was NADPH dependent. The metabolism was CYP450 mediated since incubation with HLM pre-treated with ABT (non-selective CYP450 inhibitor) resulted in no metabolism of cobimetinib *i.e.* 101% of the compound remained unchanged compared to 45% when incubated with non-ABT-pre-treated HLM.

HLM incubations with cobimetinib in the presence and absence of CYP inhibitors showed that cobimetinib appeared to be metabolised mainly *via* CYP3A4/5.

Following a single oral dose of 14C-labelled cobimetinib, the compound was extensively metabolised with about 2 and 7% of the dose excreted as parent compound in urine and faeces, respectively. In total, approximately 75% of the administered dose was excreted in faeces and about 18% in the urine.

More than 20 metabolites were identified in faeces, of which four individually accounted for 5-10% of the dose given. Three major metabolites, with plasma levels comparable to the exposure of the parent compound, were identified following a single oral 14C-labelled dose of cobimetinib. More than 20% of the radioactivity in plasma remained unextractable, with the percentage unextracted increasing with time. However, no active metabolites have been identified in circulation and two of the 3 circulating metabolites were identified as phase-2 metabolites.

Figure 3: Proposed metabolic pathways for cobimetinib GDC-0973 in humans



Note: Shown are the identified circulating metabolites and excreted metabolites that accounted for greater than 2% of the administered dose.

In vitro incubations of cobimetinib and human recombinant CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4 AND 3A5 showed CYP3A to be the main enzyme involved in the metabolism of cobimetinib. This was confirmed by an *in vivo* DDI study where the total exposure of cobimetinib increased about 7-fold when co-administered with itraconazole, a strong CYP3A inhibitor. This 7-fold increase in exposure suggests that CYP3A metabolism represents 85% of the total elimination. CYP3A4 and CYP3A5 were shown to be involved in the metabolism with about 10% and 65% of cobimetinib remaining, respectively, after 60-min incubations. Following incubations with CYP2D6 and 2C19, 80 and 85% of cobimetinib remained, respectively, while after incubations with the others >95% remained.

UGT2B7 was identified as involved in the formation of one of the major metabolites M15.

Table 28: Relative percentage of cobimetinib after 60-min incubation with HLM in the presence and absence of CYP inhibitors

CYP Inhibited	Assay Condition	Inhibitor (µM)	Relative Percentage of GDC-0973 Remaining [a]
NA	+N	NA	45.0±0.8
NA	–N	NA	102±5
All	+N+ABT [b]	1000	101±4
1A2	+N+furafylline [b]	10	42.7±1.5
2A6	+N+TCP	1	44.4±1.3
2B6/2C19	+N+ticlopidine	10	43.7±0.9
2C8	+N+quercetin	10	49.3±1.3
2C9	+N+sulfaphenazole	10	47.8±0.8
2D6	+N+quinidine	1	43.9±1.2
3A4/5	+N+ketoconazole	1	93.0±1.9
3A4/5	+N+TAO [b]	20	99.4±1.8

+N = with NADPH; -N = without NADPH;

The formation of M15 (glucuronide) was investigated, using human major recombinant UGT isozymes (1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9, 1A10. 2B4, 2B7, 2B15 and 2B17), showed UGT2B7 to be the major UGT involved in the metabolism of cobimetinib. This was also confirmed with HLM incubations with cobimetinib in the presence and absence of fluconazole.

Excretion

Cobimetinib was not classified as an OATP1B1, OATP1B3 or OCT1 substrate *in vitro* in transporter overexpressed CHO cells, respectively.

The mass-balance of excretion was studied in healthy subjects (n=6) following an oral solution of 20 mg (200 µCi) cobimetinib in an open non-randomized design. Blood/plasma, urine and faeces samples were collected regularly up to 29 days *post* dose based on exposure, excretion rate and recovery of total radioactivity.

About 60% of the radioactive dose was excreted within the first four days after dosing. The mean total recovery of radioactivity was 94(2)% with 18(2)% of the radioactive dose excreted in the urine and 77(2)% in faeces (Table 29). The fraction absorbed was estimated to 88% based on the recovery of total radioactivity and the excretion of unchanged compound and metabolites in urine and faeces.

Cobimetinib was extensively metabolised with about 2 and 7% of the dose excreted as parent compound in urine and faeces, respectively. The majority of the identified metabolites individually accounted for <5% of the administered dose.

Following the oral dose of 20 mg (200 µCi) cobimetinib in the mass-balance study (GP28369) 18% of the dose was excreted in the urine, about 2% was excreted as parent compound. The two main urine metabolites were M14 (oxidation) and M15 (glucuronide conjugate) representing about 1 and 2% of the dose, respectively. Excreted identified metabolites that individually accounted for <1% but ≥0.5% accounted for about 12% of the administered dose. The urinary elimination of cobimetinib in healthy subjects, following both an oral dose of 20 mg and an iv dose of 2 mg, was <5%.

About 77% of the administered dose was excreted in faeces, approximately 7% as parent compound. More than 20 metabolites have been identified of which four, M5, M10, M29/M62 and M56 individually accounted for 5-10% of the dose given. The average sum of metabolites accounting for ≥2% of the administered dose was calculated to 69%.

Table 29: Overview of excretion pattern in urine and faeces following an oral dose of 20 mg (200 µCi) cobimetinib

	Percentage of radioactive dose (%)		Total recovery
	Urine	Faeces	
Cobimetinib	1.6	6.6	8.2
M14	1.1	ND	1.1
M15	2.1	ND	2.1
M10	0.3	10.3	10.6
M5	–	5.2	5.2
M56	ND	5.3	5.3
M29/M62	1.0	6.9	7.9
Minor metabolites	11.8[a]	42.2[b]	54.9
Sum	17.8	76.5	94.3

ND not detected [a] identified metabolites individually accounting for <1% of the dose
[b] identified metabolites individually accounting for <5% of the dose

Dose proportionality and time dependencies

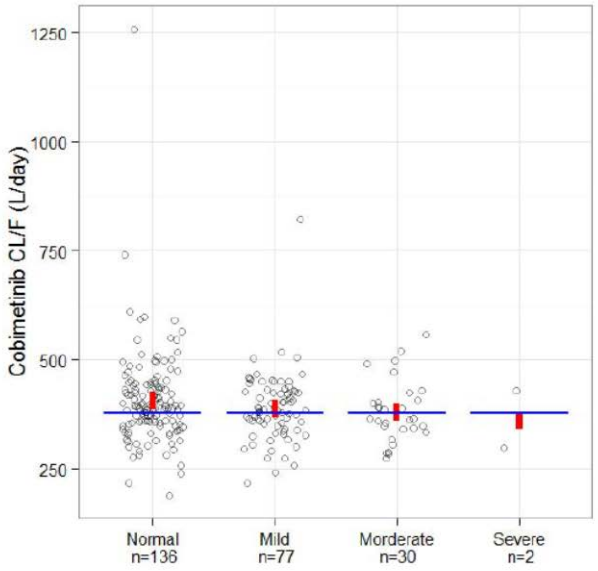
A dose escalation study to define the maximum tolerated dose (MTD) was performed in patients with solid tumours in Study MEK4592. The PK of cobimetinib was dose proportional in the clinical relevant dose range *i.e.* up to 100 mg. The exposure was about 2-3 times higher at steady state compared to a single dose (MEK4592, NO25395). The inter-individual variability in total exposure at steady state was 21-165%.

Special populations

Renal impairment

The comparison of cobimetinib CL/F in patients with different renal functions, defined according to their estimated CRCL (Normal: CRCL ≥ 90 mL/min, Mild: CRCL ≥ 60 and < 90 mL/min, Moderate: CRCL ≥ 30 and <60 mL/min, and Severe: CRCL <30 mL/min) is illustrated in Figure 4. There is limited data (n=2) in patients with severe renal impairment.

Figure 4: Comparison of Bayesian post-hoc cobimetinib CL/F for renal function



Circles are the Bayesian post-hoc PK parameter estimates from the final population PK model (CL/F). The blue lines represent the typical (population) value and the red squares are the means of the individual estimates.

Hepatic impairment

The applicant did not submit a study on hepatic impairment.

Pharmacokinetic interaction studies

Cobimetinib as inhibitor or inducer of CYP enzymes and transporters
The PK interaction potential of cobimetinib as perpetrator has been evaluated both *in vitro* and *in vivo*. *In vitro* cobimetinib showed signals on CYP1A2 and 3A4 induction as well as on inhibition of CYP3A. The *in vivo* DDI study investigating cobimetinib as a CYP3A inhibitor or inducer, did not show any differences in systemic exposure of midazolam (CYP3A substrate) when co-administered with cobimetinib compared to when dosed alone.

In vitro cobimetinib was characterized as a CYP2D6 inhibitor, however, *in vivo* the systemic exposure of dextromethorphan was comparable when administered alone and when co-administered with cobimetinib.

Cobimetinib was characterised as a BCRP inhibitor with an IC50 value of 3 µM and an inhibitor of OATP1B1, 1B3 and OCT1 at IC50 values >49 µM. Cobimetinib is not an inhibitor of OAT1, OAT3 and OCT2. Cobimetinib was not classified as a substrate of the uptake transporters OATP1B1, OATP1B3 and OCT1. Co-administration with the PPI rabeprazole did not alter the PK of cobimetinib.

Pharmacokinetics using human biomaterials

See section on metabolism and PK interaction studies.

2.4.3. Pharmacodynamics

Two studies mainly contributed to PD assessment MEK4592g (cobimetinib single agent) and NO25395 (cobimetinib in combination with vemurafenib).

Table 30: Studies that contributed to PD assessment

Study	Phase	N	Population	Cobimetinib Dose (N)	Vemurafenib Dose (N)
MEK4592g [3]	I	114	Solid tumors and RAS-or RAF-mutant tumors	QD: 14/14: 60-125 mg (41) 21/7: 2.1-80 mg (73)	
NO25395 [4]	Ib	131[a]	BRAF V600-mutation positive metastatic melanoma	QD: 14/14: 60-100 mg (22) 21/7 : 60 mg (102) 28/0 : 60 mg (7)	BID: 720 mg (51) 960 mg (78)

Evaluations of PK/pharmacodynamic (PD) relationships were conducted to quantitatively understand the exposure response (ER) relationship between cobimetinib and molecular biomarkers of drug effects (pERK, pS6, Ki-67) and 18F fluorodeoxyglucose [FDG] PET, QTc interval and efficacy/exposure relationship.

Mechanism of action

Cobimetinib is an orally available small molecule and selective allosteric inhibitor of the mitogen-activated protein kinases MEK1 and MEK2, also known as the mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase (ERK) pathway. Functional mediation of this pathway is dependent upon activity of ERK1/2 that phosphorylate protein targets in the cytoplasm and nucleus and thus induce cell-cycle progression, cell proliferation, survival and migration. ERK1/2 are the only known substrates of MEK1/2, which in turn are inhibited by cobimetinib.

Oncogenic mutations in BRAF are found in approximately 50% of malignant melanoma tumours and result in constitutive activation of the MAPK/ERK pathway in the absence of typical growth factors leading to excessive cell proliferation, and survival[3].

Cobimetinib has shown high inhibitory potency in biochemical and cell based assays, as well as broad anti-tumour activity in vivo in xenograft tumour models, including those that are mutated for BRAF and KRAS. Of note, cobimetinib has a specific mechanism of binding and inhibition of MEK1/2[21], which is suggested to be more effective for targeting BRAFV600-mediated activation of MEK, and less effective to mitigate activation of MEK by other mechanisms.

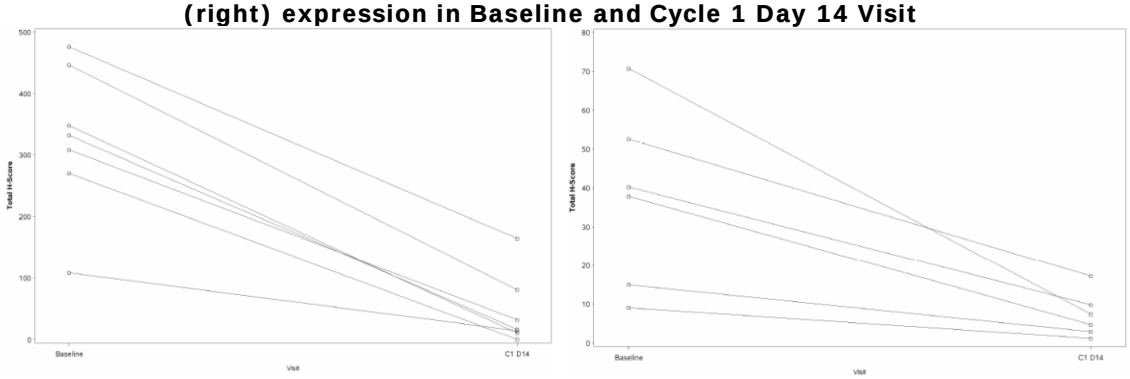
By simultaneously targeting BRAF and MEK the combination of vemurafenib and cobimetinib results in stronger inhibition of ERK signalling, greater tumour cell apoptosis and enhanced tumour responses in pre-clinical models than vemurafenib alone.

As shown in the efficacy sections below, reversal of pre-formed resistance to BRAF inhibitor therapy only occurred in a minority of cases, however. Proposed mechanisms for this finding are e.g. re-activation or re-configuration of MAPK pathway, activation of parallel signalling pathways and/or genomic diversification after disease progression on BRAF inhibitor. These mechanisms are consistent with currently known main mechanisms of resistance to BRAFi therapy[14,22, 23, 24, 25].

Pharmacodynamic effects on molecular biomarkers

In 6 patients, the PD effects of cobimetinib in combination with vemurafenib were assessed at baseline and on Cycle 1 Day 14 of combination therapy (steady-state of cobimetinib) based on paired tumour biopsies samples from both vemurafenib-PD and BRAFi-naive patients and showed reduction in pERK and pS6 levels and reduction in the number of Ki-67 positive tumour nuclei (Figure 5).

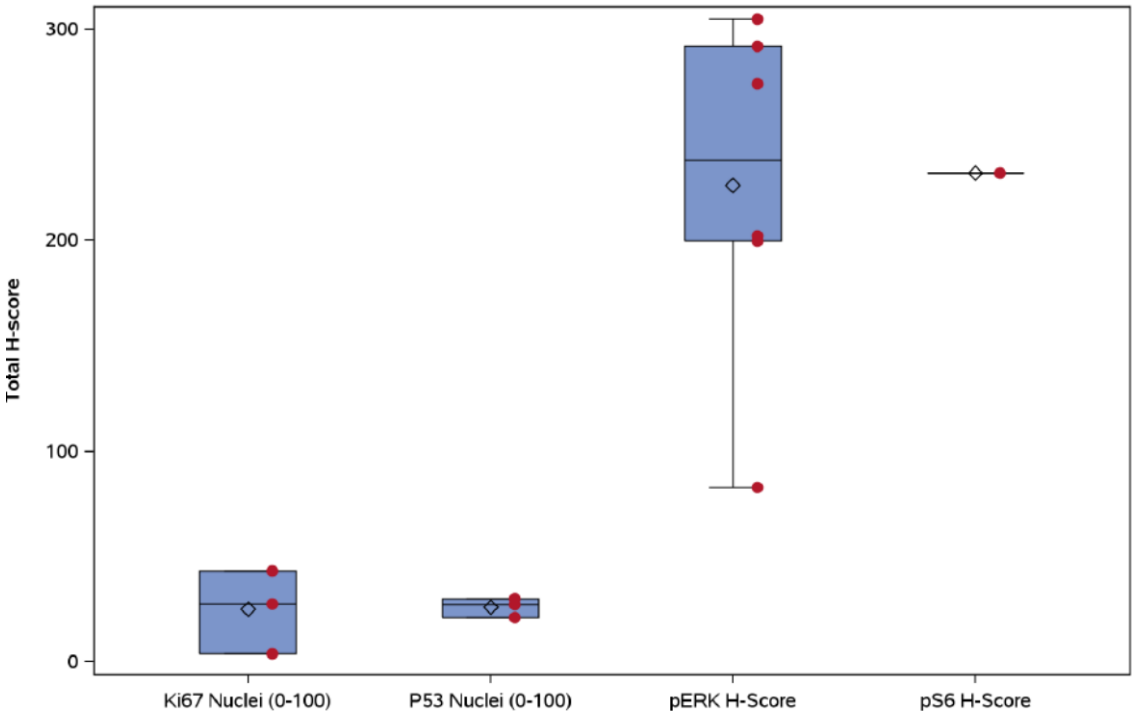
Figure 5: Signalling pathway status in paired melanoma biopsies- pERK (left) and ki67 (right) expression in Baseline and Cycle 1 Day 14 Visit



In patients who developed lesions presumed or suspected to be SCC or second primary melanomas, formalin-fixed tissue embedded in paraffin blocks was collected. Normal skin punch biopsies were obtained under local anaesthesia from all patients who developed SCC. FFPE samples from paired biopsies of SCC (or suspicious neoplasms) and normal skin were used to perform IHC analyses of pathway markers (pERK, pMEK, p53).

A total of 12 patients experienced SCC of any grade. pERK and potentially pS6 expression was high in the cuSCC specimens; Ki67 and p53 expression was low.

Figure 6: Box plot of cell signalling pathway status in cuSCC



Primary and Secondary pharmacology

Pharmacodynamic effects as measured by changes in ^{18}F-fluorodeoxyglucose (FDG)-PET Imaging after treatment

Combination of cobimetinib and vemurafenib

In the phase Ib study NO25395, the PD effect of cobimetinib in combination with vemurafenib was assessed by measuring changes in FDG uptake as characterized by the lean body mass corrected (LBM) maximum standardized uptake value (SUVmax) measurement (see Table below).

Figure 7: FDG-PET: Average LBM SUVMax at Baseline and Average of Percent Changes from Baseline of LBM SUVMax

	Baseline (Screening)	Cycle 1 (Days 10 -14)	Cycle 2 (Days 14 + 7)
Vemurafenib Progressors (N=66)			
n	63	59	50
Mean (SD)	8.75 (5.55)	-43.33 (26.00)	-33.09 (35.18)
Median	7.61	-45.90	-37.30
Min - Max	1.4 - 37.0	-87.3 - 18.3	-84.8 - 92.7
BRAFi-Naive (N=63)			
n	63	60	56
Mean (SD)	8.19 (5.00)	-65.74 (14.82)	-70.73 (17.05)
Median	7.14	-67.50	-74.05
Min - Max	1.5 - 25.0	-89.5 - -4.6	-92.6 - -13.8

On average, disease measured at baseline was more FDG-avid in vemurafenib-PD patients compared to BRAFi-naive patients.

QTc Assessment

The effects on QTc interval were assessed following administration of cobimetinib as monotherapy or in combination with vemurafenib in Study MEK4592g (in patients with advanced solid tumours) and in Study NO25395 (in patients with advanced BRAF V600-mutated melanoma), respectively. No dedicated thorough QTc study has been conducted. A summary of the data is shown in Table 31.

The number of patients with grade ≥3 QTc prolongation was 3 out of 129 safety evaluable subjects in Study NO25395 and 1 vemurafenib-PD patient and 2 BRAFi-naive patients.

Table 31: Patients with QTc interval prolongation (Study MEK4592g and Study NO25395)

	MEK4592g (Stage I) (n=36)	MEK4592g (Stage II, IA, IIA) (n=61)	NO25395 (n=125)	NO25395 BRAFi-naive (n=60)	NO25395 Vemurafenib-PD (n=65)
Maximum across all cycles					
QTc >450ms	8 (22.2%)				
QTc >480ms	0	NA	NA	NA	NA
QTc >500ms	0				
Maximum across all cycles					
QTcF >450ms		17 (27.9%)	29 (23.2%)	17 (28.3%)	12 (18.5%)
QTcF >480ms	NA	0	4 (3.2%)	1 (1.7%)	3 (4.6%)
QTcF >500ms		0	2 (1.6%)	1 (1.7%)	1 (1.5%)
Maximum QTc change from baseline					
>30 ms	7 (19.4%)	NA	NA	NA	NA
>60 ms	0				

Maximum QTcF change from baseline					
>30 ms	NA	5 (8.2%)	32 (25.6%)	23 (38.3%)	9 (13.8%)
>60 ms		0	7 (5.6%)	6 (10%)	1 (1.5%)

NA = not available; PD = pharmacodynamics.

Note: Average values of QTc and QTcF interval (absolute) presented

Exposure-QTc relationship

The concentration-response relationship for QTc (C-QTc) interval was assessed on combined data from Study MEK4592g and Study NO25395 with the use of the linear mixed-effects modelling approach as implemented within the linear mixed-effects function in R Version 2.15.1.

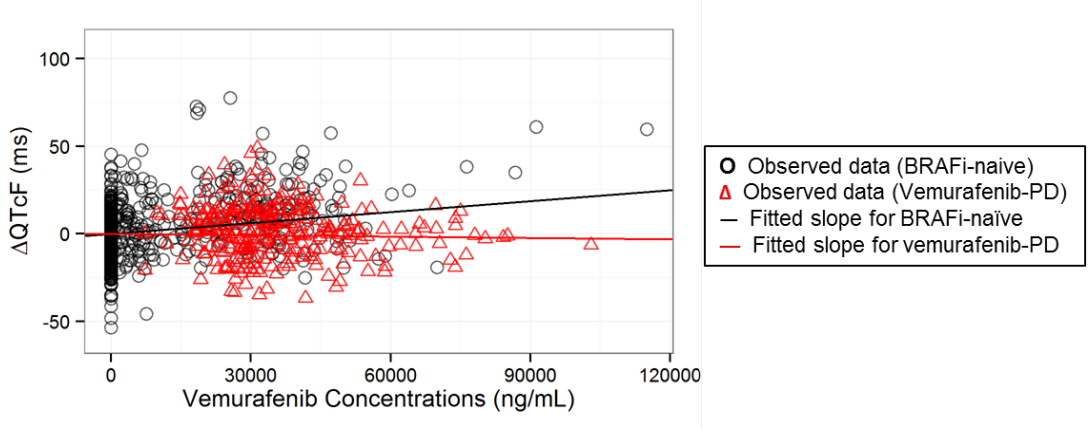
QTc interval data was available from 57 subjects that received cobimetinib alone (60 mg to 125 mg; Study MEK4592g) and 126 subjects that received cobimetinib (60 mg to 100 mg) in combination with vemurafenib (720 mg or 960 mg BID; Study NO25395). An interaction between cobimetinib and vemurafenib concentrations was tested and was not statistically significant at an alpha level of 0.05.

There was no association between cobimetinib concentrations and ΔQTcF when cobimetinib was administered alone in Study MEK4592g (slope, –0.00128 ms per ng/mL). Vemurafenib was found to prolong the ΔQTcF interval (slope, 0.207 ms per μg/mL) in BRAFi-naive subjects (see Figure below, Panel A) consistent with known vemurafenib effect on QTc interval (slope, 0.1891 ms per μg/mL). Vemurafenib-PD patients were at vemurafenib steady-state at baseline and no further increases in the QTcF interval (slope, -0.023 ms per Δg/mL) were observed.

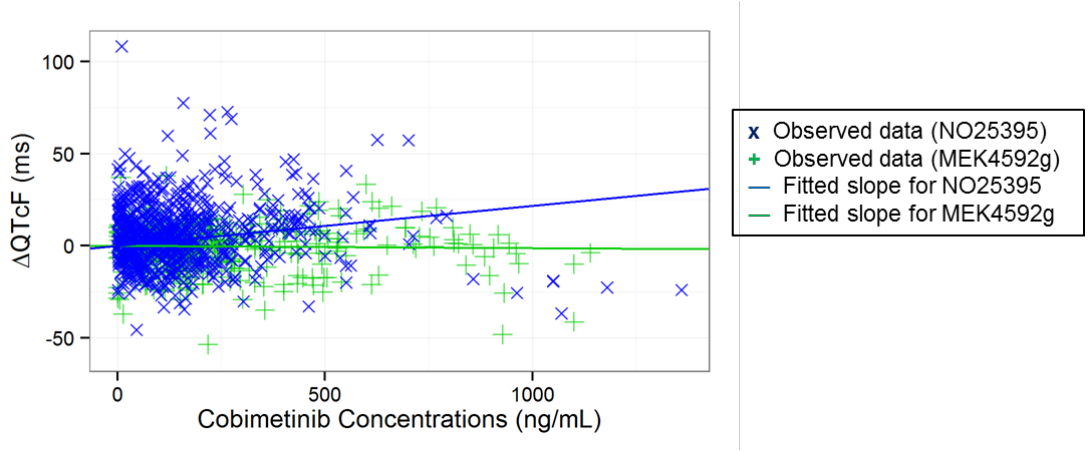
However, when cobimetinib was co-administered with vemurafenib in Study NO25395, a concentration-dependent increase in ΔQTcF was detected (slope, 0.0217 ms per ng/mL) after adjusting for vemurafenib effect in the model (see Figure below, Panel B). Similar results were obtained when data from Study NO25395 were analysed separately.

Figure 8: Exposure-Response Relationship for Baseline-Corrected QTcF Interval (Studies MEK4592g and NO25395)

A)



B)



2.4.4. Discussion on clinical pharmacology

Cobimetinib is characterized as highly soluble and moderate to highly permeable compound. The absorption was almost complete with an estimated fraction absorbed of 88% although the absolute bioavailability was calculated to be 46%. A high fat meal did not influence the systemic exposure compared to under fasted condition. Following oral dosing of 60 mg in cancer patients, cobimetinib showed a moderate rate of absorption with a median T_{max} of 2.4 hours. The mean steady-state C_{max} and AUC_{0-24} were 273 ng/mL and 4340 ng.h/mL respectively. The mean accumulation ratio at steady state was approximately 2.4-fold.

Cobimetinib has linear pharmacokinetics in the dose range of ~3.5 mg to 100 mg. The absolute bioavailability of cobimetinib was 45.9% (90% CI: 39.7%, 53.1%) in healthy subjects. A human mass balance study was conducted in healthy subjects, and showed that cobimetinib was extensively metabolised and eliminated in faeces. The fraction absorbed was ~88% indicating high absorption and first pass metabolism. The pharmacokinetics of cobimetinib are not altered when administered in the fed state (high-fat meal) compared with the fasted state in healthy subjects. Since food does not alter the pharmacokinetics of cobimetinib, it can be administered with or without food (SmPC section 5.2).

Cobimetinib is 94.8% bound to human plasma proteins *in vitro*. No preferential binding to human red blood cells was observed (blood to plasma ratio 0.93).

The volume of distribution was 1050 L in healthy subjects given an intravenous dose of 2 mg. The apparent volume of distribution was 806 L in cancer patients based on population pharmacokinetic analysis.

Cobimetinib and its metabolites were characterised in a mass balance study in healthy subjects. On average, 94% of the dose was recovered within 17 days. Cobimetinib was extensively metabolised and eliminated in faeces. Following intravenous administration of a 2 mg dose of cobimetinib, the mean plasma clearance (CL) was 10.7 L/hr. The mean apparent CL following oral dosing of 60 mg in cancer patients was 13.8 L/hr.

The mean elimination half-life following oral dosing of cobimetinib was 43.6 hours (range: 23.1 to 69.6 hours). Therefore, it may take up to 2 weeks following treatment cessation for cobimetinib to be completely removed from systemic circulation (SmPC section 5.2).

Following a single oral dose of 14C-labelled cobimetinib, cobimetinib was extensively metabolised with about 2 and 7% of dose excreted as parent compound in the urine and faeces, respectively. About 75% of dose administered was excreted in faeces.. Three metabolites were identified in plasma with individual plasma levels of >10% of total radioactivity at some time-points up to 48h post dose.

Cobimetinib is eliminated primarily via metabolism in the liver. Oxidation by CYP3A and glucuronidation by UGT2B7 appear to be the major pathways of cobimetinib metabolism. Cobimetinib is the predominant moiety in plasma. No oxidative metabolites greater than 10% of total circulating radioactivity or human specific metabolites were observed in plasma. Unchanged medicinal product in faeces and urine accounted for 6.6% and 1.6% of the administered dose, respectively, indicating that cobimetinib is primarily metabolised with minimal renal elimination (SmPC section 5.2). Serious hepatotoxicity has been added as an important potential risk. Safety in patients with moderate and severe hepatic impairment has been included as missing information in the RMP. The risk will be monitored through dose reduction and treatment discontinuation guidance for hepatic impairment and liver laboratory abnormalities as described in the SmPC Section 4.2 (Posology and method of administration). As the pharmacokinetics of cobimetinib in subjects with different degrees of hepatic function has not been investigated, the CHMP has requested the applicant to submit the results of a post-authorisation study GP29342, a Phase I, open label, single-dose study to evaluate the pharmacokinetics and safety of cobimetinib in subjects with mild, moderate or severe hepatic impairment compared to healthy subjects (deadline: 31 December 2015). This study has been included in the RMP.

In vitro investigations characterized CYP3A to be the main enzyme involved in the metabolism of cobimetinib. This was confirmed an *in vivo* DDI study where the total exposure of cobimetinib increased about 7-fold when co-administered with itraconazole, a strong CYP3A inhibitor. A 7-fold increase in exposure when inhibiting CYP3A means that CYP3A metabolism represents 85% of the total elimination. Therefore, concurrent use of strong CYP3A inhibitors during treatment with Cotellic should be avoided. Caution should be exercised if a moderate CYP3A4 inhibitor is co-administered with Cotellic. If concomitant use with a strong or moderate CYP3A inhibitor is unavoidable, patients should be carefully monitored for safety and dose modifications applied if clinically indicated (see Table 1 in section 4.2 and section 4.4).

CYP3A inhibitors

Cobimetinib is metabolized by CYP3A and cobimetinib AUC increased approximately 7- fold in the presence of a strong CYP3A inhibitor (itraconazole) in healthy subjects. The magnitude of interaction could potentially be lower in patients.

Strong CYP3A4 inhibitors (see section 4.4.): Avoid concurrent use of strong CYP3A inhibitors during treatment with cobimetinib. Strong CYP3A4 inhibitors include, but are not limited to, ritonavir, cobicistat, telaprevir, lopinavir, itraconazole, voriconazole, clarithromycin, telithromycin, posaconazole and nefazodone. If concomitant use of a strong CYP3A inhibitor is unavoidable, patients should be carefully monitored for safety. For strong CYP3A inhibitors used short-term (7 days or less), consider interrupting cobimetinib therapy during the duration of inhibitor use.

Moderate CYP3A4 inhibitors (see section 4.4.): Caution should be exercised if cobimetinib is co-administered with moderate CYP3A inhibitors. Moderate CYP3A4 inhibitors include, but are not limited to, amiodarone, erythromycin, fluconazole, miconazole, diltiazem, verapamil, delavirdine, amprenavir, fosamprenavir, imatinib. When cobimetinib is co-administered with a moderate CYP3A inhibitor, patients should be carefully monitored for safety.

Mild CYP3A4 inhibitors: Cobimetinib can be co-administered with mild inhibitors of CYP3A without dose adjustment.

When co-administered with vemurafenib, a CYP3A4 inducer, lower mean steady state concentration of cobimetinib was seen, compared to when administered alone. No conclusions can be drawn on a potential DDI effect due to few patients treated alone with cobimetinib in comparison with the combination. The steady state exposure of vemurafenib was slightly lower when co-administered with cobimetinib compared when administered alone meaning that a potential DDI between cobimetinib and vemurafenib cannot be ruled out when co-treated. *In vitro* cobimetinib showed a potential of both CYP3A induction and inhibition, however, the *in vivo* DDI study with midazolam did not show any difference in exposure if co-administered with cobimetinib. Co-administration of cobimetinib with a strong CYP3A inducer was not assessed in a clinical study, however, a reduction in cobimetinib exposure is likely. Therefore, concomitant use of moderate and strong CYP3A inducers (e.g. carbamazepine, rifampicin, phenytoin, and St. John's Wort) should be avoided. Alternative agents with no or minimal CYP3A induction should be considered. Given that cobimetinib concentrations are likely to be significantly reduced when co-administered with moderate to strong CYP3A inducers, patient's efficacy may be compromised..

P-glycoprotein inhibitors

Cobimetinib is a substrate of P-glycoprotein (P-gp). Concomitant administration of P-gp inhibitors such as ciclosporin and verapamil may have the potential to increase plasma concentrations of cobimetinib.

Effects of cobimetinib on other medicinal products

CYP3A and CYP2D6 substrates

A clinical drug-drug interaction (DDI) study in cancer patients showed that plasma concentrations of midazolam (a sensitive CYP3A substrate) and dextromethorphan (a sensitive CYP2D6 substrate) were not altered in the presence of cobimetinib.

CYP1A2 substrates

In vitro, cobimetinib is a potential inducer of CYP1A2. No clinical DDI studies have been conducted to assess the clinical relevance of this finding. The drug-drug interactions (with CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYPC19 and CYP2D6) have been included in the RMP as missing information. The potential of cobimetinib to act as a time-dependent inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9,

CYP2C19 and CYP2D6 will be evaluated in an *in vitro* Study 15-1983 to determine if cobimetinib is a time-dependent inhibitor of CYP genes. The CHMP has requested the submission of the results of this study as a post-authorisation measure in the RMP (deadline: 31 December 2015). It is therefore recommended that women of childbearing potential should be advised to use two effective contraceptive methods, such as a condom or other barrier method (with spermicide, if available) during treatment with Cotellic and for at least three months following treatment discontinuation.

BCRP substrates

In vitro, cobimetinib is a moderate inhibitor of BCRP (Breast Cancer Resistance Protein). No clinical DDI studies have been conducted to assess these finding, and relevant BCRP inhibition at intestinal level cannot be ruled out.

In vitro studies show that cobimetinib is not a substrate of the liver uptake transporters OATP1B1, OATP1B3 and OCT1, however, it weakly inhibits these transporters. The clinical relevance of these findings has not been investigated. Cobimetinib is not an inhibitor of OAT1, OAT3 or OCT2. It is unlikely that cobimetinib would alter the hepatic uptake or renal excretion of drugs that are substrates of these transporters (SmPC section 4.5).

As renal clearance plays a minimal role in the elimination of cobimetinib, a significant effect of renal function on the exposure is not expected. However, even if the drug is eliminated mainly by metabolism, PK characterization in severe renal impairment should always be considered as severe renal impairment may affect the PK by diverse mechanisms. Based on preclinical data and the human mass balance study, cobimetinib is mainly metabolised, with minimal renal elimination. No formal pharmacokinetic study has been conducted in patients with renal impairment. A population pharmacokinetic analysis using data from 151 patients with mild renal impairment (creatinine clearance (CRCL) 60 to less than 90 mL/min), 48 patients with moderate renal impairment (CRCL 30 to less than 60 mL/min), and 286 patients with normal renal function (CRCL greater than or equal to 90 mL/min), showed that CRCL had no meaningful influence on exposure of cobimetinib (SmPC section 5.2).

Mild to moderate renal impairment does not influence cobimetinib exposure based on the population pharmacokinetic analysis. There are minimal data for Cotellic in patients with severe renal impairment.

No pharmacokinetic data in subjects with hepatic impairment are available.

No significant covariates necessitating dose-adjustment were identified in the population pharmacokinetic model. Gender does not have an effect on the exposure of cobimetinib, based on a population pharmacokinetic analysis including 210 women and 277 men (SmPC section 5.2). Age does not have an effect on the exposure of cobimetinib, based on a population pharmacokinetic analysis including 133 patients ≥ 65 years of age (SmPC section 5.2).

No dose adjustment is required in patients aged ≥65 years old (SmPC section 4.2). No dose adjustment is recommended in patients with mild or moderate renal impairment based on population pharmacokinetic analysis (SmPC sections 4.2 and 5.2). There are minimal data for Cotellic in patients with severe renal impairment. Cotellic should be used with caution in patients with severe renal impairment. The safety and efficacy of Cotellic has not been established in patients with hepatic impairment (SmPC sections 4.2 and 5.2). There are no pharmacokinetic data in patients with moderate or severe hepatic impairment. Cotellic should be used with caution in patients with moderate to severe hepatic impairment.

Based on a population pharmacokinetic analysis, gender, race, ethnicity, baseline ECOG, mild and moderate renal impairment did not affect the pharmacokinetic of cobimetinib. Baseline age and baseline body weight were identified as statistically significant covariates on cobimetinib clearance and volume of distribution respectively. However, sensitivity analysis suggests neither of these covariates had clinically significant impact on steady state exposure (SmPC section 5.2).

Interaction studies have only been performed in adults (SmPC section 4.5). No studies have been conducted to investigate the pharmacokinetics of cobimetinib in paediatric patients (SmPC section 5.2).

There is no evidence of any clinically significant drug-drug interaction between cobimetinib and vemurafenib in unresectable or metastatic melanoma patients and therefore no dose adjustments is recommended (SmPC section 4.4).

Several biomarkers were tested in an attempt to assess their predictive value. The biomarkers pERK, pS6, PTEN, and Ki67 were measured at baseline, however there was not a clear marker to distinguish responders from non-responders.

Pharmacodynamic effects of cobimetinib in combination with vemurafenib were shown in a limited number of paired samples by changes in biomarker levels (pERK, pS6, Ki67) between baseline and Cycle 1 Day 14. These changes indicated a reduction of signalling within pathway translated into reduction in ERK phosphorylation.

Cutaneous SCC were characterized using molecular analyses in few cuSCC samples. With the samples available in this study, pERK was higher in the cuSCC specimens and p53 expression was lower. However, the small sample size did not allow the conclusive investigation.

2.4.5. Conclusions on clinical pharmacology

The studies submitted as part of the clinical pharmacology were considered acceptable to investigate the PK and PD aspects of the combination of cobimetinib and vemurafenib.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- The PK interaction potential of cobimetinib has not been completely evaluated. According to the EU guideline on DDI, all important CYPs should be evaluated for time-dependent in vitro. The in vitro time-dependent inhibition potential of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYPC19 and CYP2D6 has not been evaluated. The applicant is requested to submit the results of the in vitro CYP time-dependent inhibition study (15-1983). Deadline: 31 December 2015
- The pharmacokinetics of cobimetinib in subjects with different degrees of hepatic function has not been investigated. Therefore, the applicant is requested to submit the results of study GP29342: A Phase I, open label, single-dose study to evaluate the pharmacokinetics and safety of cobimetinib in subjects with mild, moderate or severe hepatic impairment compared to healthy subjects. Deadline: 31 December 2015

2.5. Clinical efficacy

2.5.1. Dose response study

The applicant did not submit dedicated dose response studies.

The single-agent MEK4592g study (a Phase I Dose-Escalation Study of the Safety and Pharmacokinetics of Cobimetinib Administered Orally Daily to Subjects with Solid Tumors) established the maximum tolerated dose (MTD) of cobimetinib at 100 mg daily when delivered on a 14/14 schedule and 60 mg daily when delivered on a 21/7 schedule. Exposures (as measured by Cmax and AUC parameters) increased proportionally with dose up to a dose of 100 mg QD and supported the use of either the 14/14 or the 21/7 regimen.

Study NO25395 (BRIM7) determined the MTD and the recommended Phase 3 dose and schedule of the combination as vemurafenib 960 mg BID and cobimetinib 60 mg daily 21/7. At that dose and schedule of the combination, both drugs were delivered at their respective single agent MTDs and at the highest dose of both agents delivered concurrently. Furthermore, the 21/7 dosing schedule allowed for a more prolonged exposure of cobimetinib during a treatment cycle.

2.5.2. Main study

GO28141 (coBRIM) – A Phase III double-blind, placebo-controlled study of vemurafenib versus vemurafenib plus GDC-0973 in previously untreated BRAF600-mutation positive patients with unresectable locally advanced or metastatic melanoma

Methods

Study Participants

Key eligibility criteria for Study GO28141 ("coBRIM") included:

- Histologically confirmed melanoma, either unresectable Stage IIIC or Stage IV metastatic melanoma, as defined by the American Joint Committee on Cancer 7th edition. Unresectability of Stage IIIC disease must have confirmation from a surgical oncologist.
- No prior therapy for locally advanced unresectable or metastatic disease. Prior adjuvant therapy (including immunotherapy such as ipilimumab) is allowed.
- Documentation of BRAFV600 mutation-positive status in melanoma tumour tissue (archival or newly obtained tumour samples) using the cobas 4800 BRAF V600 mutation test.
- Measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1
- Adequate hematologic, liver, renal and cardiac function

Full inclusion criteria are shown in Table 32 below.

Table 32: Inclusion and exclusion criteria in Study GO28141

Study GO28141 (coBRIM)	
Inclusion Criteria	**Exclusion Criteria**
Disease-Specific Inclusion Criteria: 1. Patients with histologically confirmed melanoma, either unresectable Stage IIIc or Stage IV metastatic melanoma, as defined by the American Joint Committee on Cancer 7th edition. Unresectability of Stage IIIc disease must have confirmation from a surgical oncologist. 2. Patients must be naïve to treatment for locally advanced unresectable or metastatic disease (i.e., NO prior systemic anti-cancer therapy for advanced disease; Stage IIIc and IV). Prior adjuvant therapy (including immunotherapy, e.g., ipilimumab) is allowed. 3. Documentation of BRAFV600 mutation-positive status in melanoma tumour tissue (archival or newly obtained tumour samples) using the cobas 4800 BRAF V600 mutation test 4. Measurable disease per RECIST v1.1 5. Eastern Cooperative Oncology Group Performance Status of 0 or 1 6. Consent to provide archival tissue (either a paraffin-embedded tissue block or up to 20 unstained slides) for biomarker analyses 7. Consent to undergo tumour biopsies of accessible lesions on Cycle 2 Day 15 and at progression for biomarker analyses to explore intrinsic and acquired resistance *General Inclusion Criteria:* 8. Male or female patient aged ≥ 18 years 9. Able to participate and willing to give written informed consent prior to performance of any study-related procedures and to comply with the study protocol 10. Life expectancy ≥ 12 weeks 11. Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to first dose of study drug treatment: • ANC ≥ 1.5 × 109/L • Platelet count ≥ 100× 109/L • Haemoglobin ≥ 9 g/dL • Albumin ≥ 2.5 g/dL • Bilirubin ≤ 1.5 × the upper limit of normal (ULN) • AST, ALT, and alkaline phosphatase ≤ 3×ULN, with the following exceptions: o Patients with documented liver metastases: AST and/or ALT ≤ 5×ULN	*Cancer-Related Exclusion Criteria:* 1. History of prior RAF or MEK pathway inhibitor treatment 2. Palliative radiotherapy within 14 days prior to the first dose of study treatment 3. Major surgery or traumatic injury within 14 days prior to first dose of study treatment 4. Patients with active malignancy (other than BRAF–mutated melanoma) or a previous malignancy within the past 3 years are excluded; except for patients with resected melanoma, resected BCC, resected cutaneous SCC, resected melanoma in-situ, resected carcinoma in-situ of the cervix, and resected carcinoma in-situ of the breast. 5. History of isolated elevation in prostate-specific antigen in the absence of radiographic evidence of metastatic prostate cancer is allowed. *Exclusion Criteria Based on Organ Function* *Ocular:* 6. History of or evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for neurosensory retinal detachment / central serous chorioretinopathy (CSCR), retinal vein occlusion (RVO), or neovascular macular degeneration 7. The risk factors for RVO are listed below. Patients will be excluded if they currently have the following conditions: a) Uncontrolled glaucoma with intra-ocular pressures ≥21mmHg b) Serum cholesterol ≥Grade 2 c) Hypertriglyceridemia ≥ Grade 2 d) Hyperglycemia (fasting) ≥Grade 2 *Cardiac:* 8. History of clinically significant cardiac dysfunction, including the following: a) Current unstable angina b) Symptomatic congestive heart failure of New York Heart Association class 2 or higher (Appendix 7) c) History of congenital long QT syndrome or mean (average of triplicate measurements) QTcF ≥ 450 msec at baseline or uncorrectable abnormalities in serum electrolytes (sodium, potassium, calcium, magnesium, phosphorus). Please refer to Section 4.5.1.11 d) Uncontrolled hypertension≥ Grade 2 (patients with a history hypertension controlled with anti-hypertensives to ≤ Grade 1 are eligible)

o Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5×ULN • Serum creatinine ≤ 1.5 × ULN or creatinine clearance (CrCl) ≥ 40 mL/min on the basis of measured CrCl from a 24-hour urine collection or Cockroft-Gault glomerular filtration rate estimation: (140 − age) × (weight in kg) × (0.85 if female) 72 × (serum creatinine in mg/dL) 12. Female patients of childbearing potential and male patients with partners of childbearing potential must agree to always use 2 effective forms of contraception during the course of this study and for at least 6 months after completion of study therapy. • Females of childbearing potential are defined as sexually mature women without prior oophorectomy or hysterectomy who have had menses within the last 12 months. • Females are not considered to be of childbearing potential if amenorrheic for > 12 months and follicle-stimulating hormone (FSH) level ≥ 40 IU/L. • For females who have been amenorrheic for ≥ 2 years, the requirement for FSH measurement at screening will be waived. • Effective forms of contraception include surgical sterilization, a reliable barrier method with spermicide, birth control pills, or contraceptive hormone implants. Please note that potential interactions between vemurafenib and hormonal contraceptives may decrease the effectiveness of hormonal contraceptives. • Male patients who are surgically sterilized are required to use barrier methods of contraception. 13. Negative serum pregnancy test within 14 days prior to commencement of dosing in women of childbearing potential 14. Absence of any psychological, familial, sociological, or geographical condition that potentially hampers compliance with the study protocol and follow-up after treatment discontinuation schedule; those conditions should be discussed with the patient before trial entry.	e) Left ventricular ejection fraction (LVEF) below institutional lower limit of normal (LLN) or below 50%, whichever is lower *Central Nervous System:* 9. Patients with active CNS lesions (carcinomatous meningitis) are excluded. However, patients are eligible if: a) All known CNS lesions have been treated with stereotactic therapy or surgery, AND b) There has been no evidence of clinical and radiographic disease progression in the CNS for ≥ 3 weeks after radiotherapy or surgery c) Whole brain radiotherapy is not allowed, with the exception of patients who have had definitive resection or stereotactic therapy of all radiologically detectable parenchymal brain lesions. *General Exclusion Criteria:* 10. Current severe, uncontrolled systemic disease 11. History of malabsorption or other condition that would interfere with absorption of study drugs 12. Pregnant, lactating, or breast feeding 13. Unwillingness or inability to comply with study and follow-up procedures 14. The following foods/supplements are prohibited at least 7 days prior to initiation of and during study treatment: a) St. John's wort or hyperforin (potent CYP3A4 enzyme inducer) b) Grapefruit juice (potent cytochrome P450 CYP3A4 enzyme inhibitor).

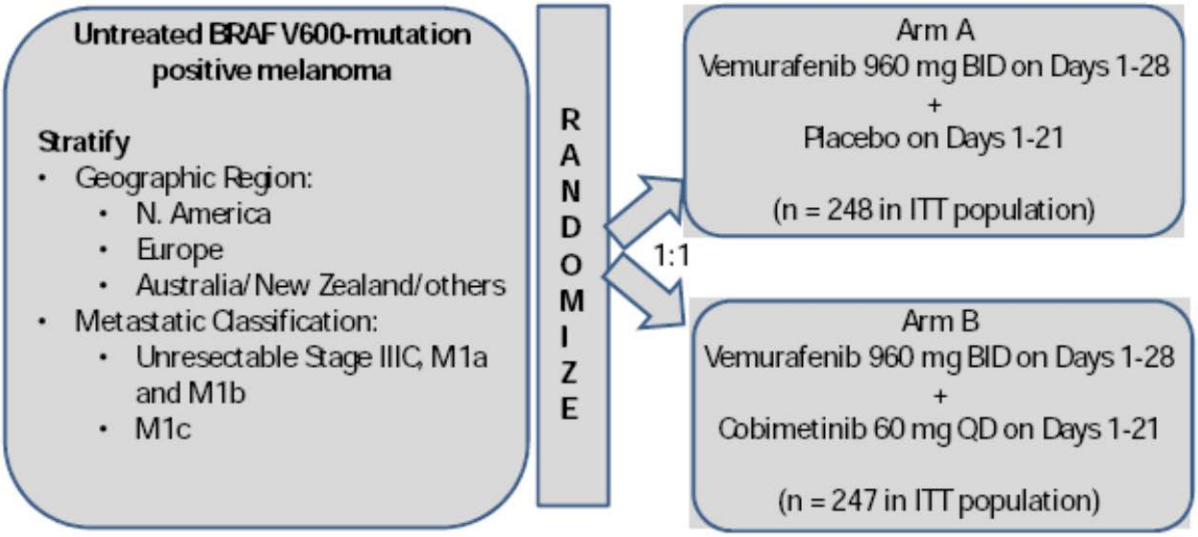
Treatments

Patients were randomized in a 1:1 ratio to receive treatment with one of the following regimens, as illustrated in Figure 9:

• Arm A (control arm): vemurafenib 960 mg by mouth (PO) twice daily (BID) on Days 1−28 and placebo PO once daily (QD) on Days 1−21 of each 28-day treatment cycle

• Arm B (investigational arm): vemurafenib 960 mg PO BID on Days 1−28 and cobimetinib 60 mg PO QD on Days 1−21 of each 28-day treatment cycle

Figure 9: Study design



BID = twice daily; ITT = intent-to-treat; QD = once daily

Treatment was supposed to continue until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurred earliest. Patients in the placebo plus vemurafenib arm were not eligible to cross over to the cobimetinib plus vemurafenib arm.

Objectives

Efficacy objectives (primary and secondary)

The primary efficacy objective was to evaluate the efficacy of vemurafenib in combination with cobimetinib, compared with vemurafenib and placebo, in previously untreated BRAFV600 mutation-positive patients with unresectable locally advanced or metastatic melanoma.

The key secondary objectives were as follows: to evaluate the efficacy of vemurafenib in combination with cobimetinib, compared with vemurafenib and placebo, in previously untreated BRAFV600 mutation-positive patients with unresectable locally advanced or metastatic melanoma, as measured by overall survival (OS), objective response rate (ORR), duration of response (DOR), and PFS as assessed by independent review; to evaluate health-related quality of life (HRQL) in patients receiving vemurafenib and cobimetinib versus vemurafenib and placebo, as measured by the European Organization for Research and Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and the EuroQol 5 dimension (EQ-5D) questionnaire.

Safety Objective

To characterise the toxicity profile of patients receiving vemurafenib and cobimetinib versus vemurafenib and placebo.

Outcomes/endpoints

Primary endpoint

Investigator assessed PFS, defined as the time from randomization to the first occurrence of disease progression (as determined by the investigator using RECIST v1.1) or death from any cause, whichever came first.

Secondary endpoint

Overall survival (OS, defined as the time from randomization until the date of death from any cause), objective response rate (ORR), duration of response (DoR, defined as the time from first occurrence of a documented confirmed objective response until the time of disease progression, as determined by investigator review of tumour assessments with use of RECIST v1.1, or death from any cause during the study), Time to objective response (TTR, defined as the time from randomization to the date of the first CR or PR, confirmed), and independent review facility (IRF)--assessed PFS.

ORR was determined as the Investigator-based (confirmed) Best Overall Response Rate (BORR), defined as a complete response (CR) or partial response (PR) per RECIST v 1.1. The best overall response of CR or PR were determined by two consecutive investigator assessments that were 4 or more weeks apart. In the case of stable disease, measurements must have met the SD criteria at least once after study entry (randomisation) at a minimum interval not less than 6 weeks. Evaluable patients who did not meet these criteria were considered non-responders; this includes patients who never received study treatment and treated patients for whom post-baseline tumour assessment was not performed. No formal hypothesis testing was performed for DoR and Time to response, which were based on non-randomised patient subsets.

Efficacy exploratory endpoints

Efficacy exploratory analyses included PFS rates and OS rates at fixed time-points (e.g., 3, 6, 9, 12 months), as well as time to response.

Safety endpoints

Incidence, nature, and severity of adverse events (AEs) and serious adverse events (SAEs), graded according to NCI CTCAE v4.0. Adverse events of special interest (AESIs) (see safety section). Changes in vital signs, ECGs, and clinical laboratory results during the course of study.

Sample size

The study was designed to provide > 95% power to detect an improvement in median PFS from 6 months in the placebo plus vemurafenib arm to 11 months in the cobimetinib plus vemurafenib arm, corresponding to a hazard ratio (HR) of 0.55. Approximately 500 patients were to be randomized; the final analysis of PFS was to take place when approximately 206 PFS events had occurred. The Type 1 error for the analysis of the primary endpoint of PFS was 0.05 (2-sided). No interim analyses of the primary endpoint (PFS) and the secondary endpoint BORR were to be performed.

Three OS analyses (two interim analyses and one final analysis) were originally planned as following: the first OS interim analysis at the time of the primary PFS analysis (projected to occur approximately 16 months after the first patient was randomised), the second OS interim analysis after the occurrence of 256 events (projected to occur at approximately 27 months after the first patient was randomised), and the final analysis of OS after the occurrence of 385 deaths (projected to occur at approximately 46 months after the first patient was randomised). A total of 385 deaths provides approximately 80% power to detect an improvement in median OS from 15 months in the placebo plus vemurafenib arm to

20 months in the cobimetinib plus vemurafenib arm (corresponding to a HR for death of 0.75) at an overall two-sided alpha level of 0.05 significance. This original plan was changed (after SAP Amendment v3) and the final OS analysis was performed after the occurrence of 250 events (projected to occur at approximately 31 months after the first patient was randomised). A total of 250 deaths provided approximately 80% power to detect an improvement in median OS from 15 months in the placebo plus vemurafenib arm to 21.4 months in the cobimetinib plus vemurafenib arm (corresponding to a HR for death of 0.70) at an overall two-sided alpha level of 0.05 significance.

Randomisation

Patients were randomised to one of the two treatment arms through use of an interactive voice response system (IVRS). Randomization was stratified by metastatic classification (unresectable Stage IIIc, M1a, and M1b or Stage M1c) and geographic region (North America, Europe, Australia/New Zealand/others). A stratified permuted block randomisation scheme was used to obtain approximately a 1:1 allocation between the two treatment groups.

Blinding (masking)

The study was a double blinded study.

Statistical methods

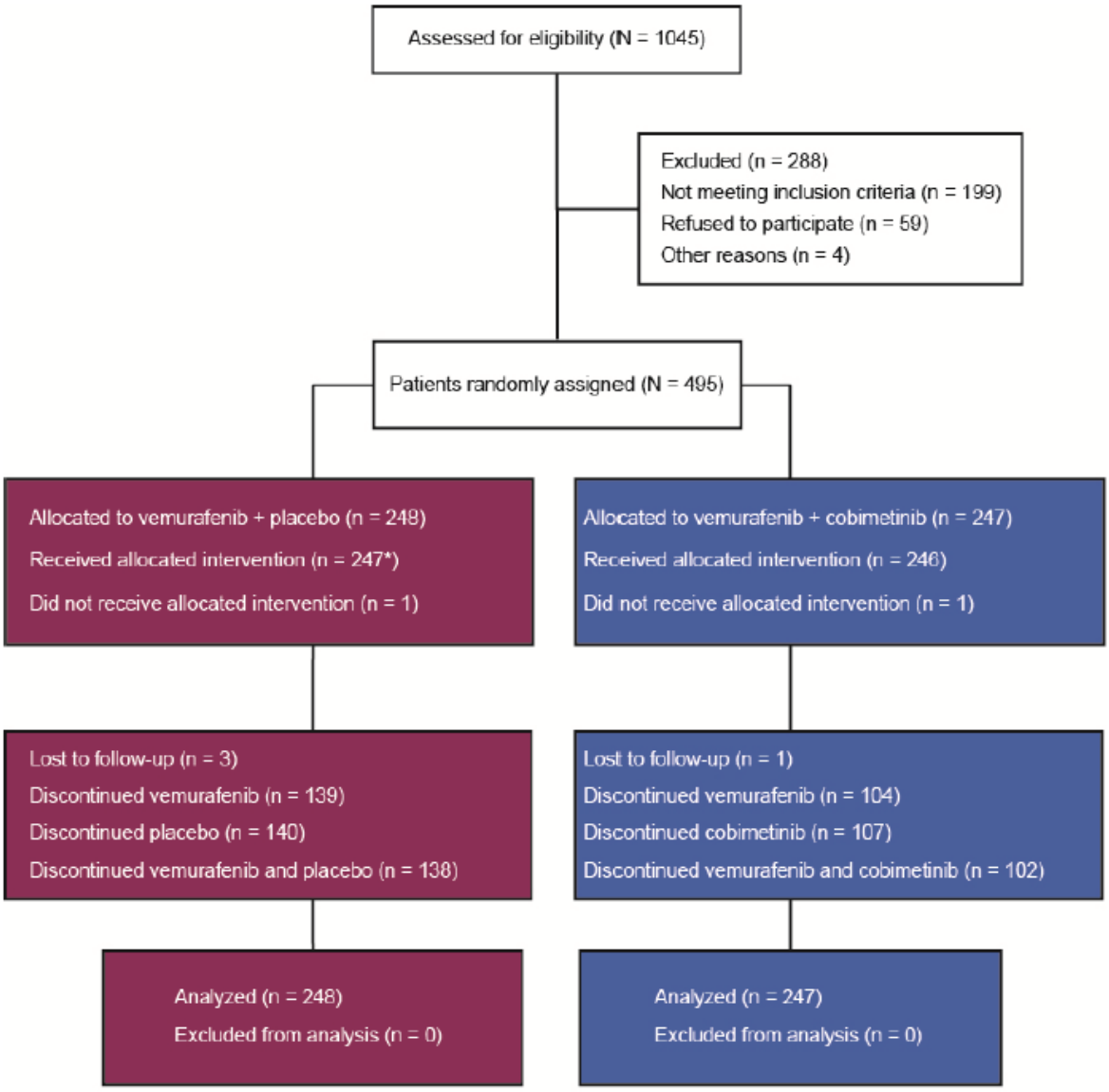
The statistical hypothesis of this study was as follows:
H0: $PFS_{(Arm\ A)} = PFS_{(Arm\ B)}$
H1: $PFS_{(Arm\ A)} \neq PFS_{(Arm\ B)}$

The primary analysis was a comparison of PFS between the two treatment arms with use of a stratified log-rank test at an overall 0.05 significance level (2-sided). The hazard ratio for PFS was estimated using a stratified Cox model. Two-sided 95% confidence intervals for the hazard ratio was provided. The stratified analyses will incorporate 2 stratification factors: geographic region and metastatic classification (see Randomisation above). Results from an unstratified log-rank test and the unstratified hazard ratio will be presented. Kaplan-Meier methodology was used to estimate median PFS for each treatment arm. P-values for ORR were calculated using chi-square with Schouten correction.

The study was designed to provide greater than 95% power to detect an improvement in median PFS from 6 months in the vemurafenib + placebo arm to 11 months in the vemurafenib + cobimetinib arm, corresponding to a hazard ratio (HR) of 0.55. Patients continued to be followed until death after the primary analysis of PFS. Three OS analyses (two interim analyses and one final analysis) were planned, the final analysis of OS will be performed after the occurrence of approximately 250 OS events (after SAP Amendment v3) i.e. after the death of approximately 50% of patients.

Results

Participant flow



8 patients mistakenly received cobimetinib at least 1 cycle according to the database at clinical cutoff date May 9, 2014.

Recruitment

The first patient entered the study on 08 January 2013 (FPI) and the last patient entered the study on 31 January 2014 (LPI). The data cut-off date for the primary analyses was 9 May 2014; an updated analysis of PFS, ORR, and OS from the Study GO28141 (data cut-off date 16 January 2015) and an updated safety analysis for both Study GO28141 (data cut-off date 19 September 2014) and Study NO25395 (cut-off 5 September 2014) were also provided.

Conduct of the study

Protocol Amendments

The original protocol was issued on 3 August 2012 and 3 amendments were made to it. The key changes are reported below.

- Protocol Version 3 (24 April 2013), to include the following changes: added PFS as assessed by independent review as a secondary endpoint; clarified exclusion criteria 4 to allow patients with previously resected early stage melanoma into the study; added cardiac events/Grade ≥ 2 LVEF reduction as AESIs; revised guidelines for cases of emergency unblinding to allow investigators the ability to unblind without the Sponsor's approval; change in reporting windows for pregnancy and pregnant partners, for LVEF, dermatology, and ophthalmology exams after Cycle 2; revised guidelines on corrected QT interval (QTc) monitoring/cardiac consult to be more conservative; updated safety information on the cobimetinib plus vemurafenib combination; further clarified procedures described in the protocol to enhance readability and understanding.

- Protocol Version 4 (12 September 2013) to include the following changes: updated safety information for consistency with the vemurafenib Investigator's Brochure; updated and further clarified procedures described in the protocol to enhance readability and understanding.

- Protocol Version 4 Addendum 1 (17 March 2014), to include lipase and amylase testing to confirm diagnosis in suspected cases of pancreatitis.

No changes were made to planned data analyses, with the following exceptions:

- Repeated measures mixed-effects models for PRO were not performed, as no clinically meaningful changes were observed from the descriptive statistics and the analyses of change from baseline.
- The sensitivity analysis of PFS censored for missing visits was not performed as the number of patients with missing visits was very low
- Unstratified and stratified analyses of OS censored for use of subsequent anti-cancer therapy were performed but were not included in the report, as the quantity of available data (i.e. number of censored patients) was not sufficient for a meaningful analysis
- A post hoc analysis was performed to evaluate the magnitude of the best target lesion response

Study GO28141 SAP Amendments:

- SAP Version 2 (22 June 2014), the definition of the analysis population for best overall response rate was changed from the definition in the original SAP. The former definition specified that patients who were randomized at least 18 weeks before the data cutoff date were to be included in the analysis. The revised definition specified that all randomized patients, regardless of whether or not study treatment was received, would be included in the analysis. Additionally, the subgroup analysis for time since metastatic disease diagnosis (< 6 months, ≥ 6 months) was deleted because the information required for this analysis (the date of metastatic diagnosis) was not collected.

- SAP Version 3 (23 February 2015), the final OS analysis plan was changed to perform the final OS analysis after the occurrence of 250 deaths from the initial plan of 385 deaths.

Protocol violations

A total of 26 patients, 12 (4.9%) in the cobimetinib plus vemurafenib arm and 14 (5.6%) in the placebo plus vemurafenib arm) had at least one violation of the inclusion or exclusion criteria. The most common deviations from entry criteria were history of clinically significant cardiac dysfunction (exclusion criterion 8: 12 patients, 6 (2.4%) in each arm); and risk factors for RVO (exclusion criterion 7: 4 patients, 1 and 3 in the respective arms).

Another 36 patients had procedural deviations during the course of the study. The most common of these was lack of patient compliance with the dosing regimen (e.g., off treatment longer than 28 days, more than 7 days off between treatment cycles; 13 patients), followed by deviations in the ECG procedures (e.g. ECGs not done at two consecutive visits; 8 patients).

Baseline data

Table 33: Demographic Characteristics (ITT Population) – Study GO28141

	Vemurafenib + Placebo (N=248)	Vemurafenib + Cobimetinib (N=247)	All Patients (N=495)
Age (yr)			
n	248	247	495
Mean (SD)	55.3 (13.8)	54.9 (14.0)	55.1 (13.9)
Min - Max	25 - 85	23 - 88	23 - 88
Median	55.0	56.0	55.0
Age group (yr)			
n	248	247	495
< 65	179 (72.2%)	183 (74.1%)	362 (73.1%)
65 - 74	46 (18.5%)	44 (17.8%)	90 (18.2%)
>= 75	23 (9.3%)	20 (8.1%)	43 (8.7%)
Sex			
n	248	247	495
Male	140 (56.5%)	146 (59.1%)	286 (57.8%)
Female	108 (43.5%)	101 (40.9%)	209 (42.2%)
Race			
n	248	247	495
White	235 (94.8%)	227 (91.9%)	462 (93.3%)
Native Hawaiian or Other Pacific Islander	1 (0.4%)	0	1 (0.2%)
Asian	0	1 (0.4%)	1 (0.2%)
Multiple	1 (0.4%)	1 (0.4%)	2 (0.4%)
Other	2 (0.8%)	2 (0.8%)	4 (0.8%)
Unknown	9 (3.6%)	16 (6.5%)	25 (5.1%)
Geographic Region			
Australia/New Zealand/Others	38 (15.3%)	40 (16.2%)	78 (15.8%)
Europe	184 (74.2%)	182 (73.7%)	366 (73.9%)
N. America	26 (10.5%)	25 (10.1%)	51 (10.3%)
Metastatic Classification			
Stage IIIc/M1a/M1b	95 (38.3%)	101 (40.9%)	196 (39.6%)
Stage M1c	153 (61.7%)	146 (59.1%)	299 (60.4%)
Weight (kg) at baseline			
n	245	245	490
Mean (SD)	78.93 (16.97)	81.40 (19.01)	80.16 (18.04)
Min - Max	42.0 - 148.1	48.5 - 185.0	42.0 - 185.0
Median	77.70	78.80	78.00
Height (cm) at baseline			
n	239	241	480
Mean (SD)	170.44 (10.04)	171.31 (8.87)	170.87 (9.47)
Min - Max	148.0 - 200.0	144.8 - 196.0	144.8 - 200.0
Median	170.80	171.00	171.00

Table 34: Disease Characteristics at Baseline (ITT Population) - Study GO28141

	Vemurafenib + Placebo (N=248)	Vemurafenib + Cobimetinib (N=247)	All Patients (N=495)
Time from melanoma first diagnosed (Months)			
n	245	240	485
Mean (SD)	40.96 (48.25)	53.45 (68.50)	47.14 (59.41)
Min - Max	0.1 - 337.5	0.4 - 420.8	0.1 - 420.8
Median	25.13	28.11	25.92
Stage of melanoma at time of study randomization			
n	248	247	495
IIIc	13 (5.2%)	21 (8.5%)	34 (6.9%)
M1a	40 (16.1%)	40 (16.2%)	80 (16.2%)
M1b	42 (16.9%)	40 (16.2%)	82 (16.6%)
M1c	153 (61.7%)	146 (59.1%)	299 (60.4%)
ECOG PS at baseline			
n	244	243	487
0	164 (67.2%)	184 (75.7%)	348 (71.5%)
1	80 (32.8%)	58 (23.9%)	138 (28.3%)
2	0	1 (0.4%)	1 (0.2%)
Prior Treated Brain Metastasis			
n	248	247	495
Yes	2 (0.8%)	1 (0.4%)	3 (0.6%)
No	246 (99.2%)	246 (99.6%)	492 (99.4%)
Screening Serum Lactate Dehydrogenase			
n	242	242	484
LDH Normal	138 (57.0%)	130 (53.7%)	268 (55.4%)
LDH Elevated	104 (43.0%)	112 (46.3%)	216 (44.6%)
BRAF mutation status			
n	206 (83.1%)	194 (78.5%)	400 (80.8%)
V600E	174 (70.2%)	170 (68.8%)	344 (69.5%)
V600E	32 (12.9%)	24 (9.7%)	56 (11.3%)
Prior Adjuvant Therapy			
n	248	247	495
Yes	24 (9.7%)	24 (9.7%)	48 (9.7%)
No	224 (90.3%)	223 (90.3%)	447 (90.3%)

Numbers analysed

Table 35: Analysis populations (coBRIM) - Study GO28141

Analysis Population	Placebo + Vemurafenib	Cobimetinib + Vemurafenib	All Patients
Intent-to Treat (ITT)	248	247	495
Safety-Evaluable*	239	254	493
Patient Reported Outcome (PRO)	209	211	420

*The reasons for the difference between the safety-evaluable and ITT populations are as follows:

- Two patients (one in each study arm) received no study drug.
- Eight patients randomized to the ITT placebo plus vemurafenib arm were identified as having received one or more doses of cobimetinib and were therefore included in the cobimetinib plus vemurafenib arm for safety analyses.

ITT: all randomized patients, regardless of whether or not study treatment was received

Safety-Evaluable: all patients who received at least one dose of study treatment (i.e. cobimetinib/placebo, or vemurafenib)

PRO: all patients who had a baseline assessment and at least one post-baseline assessment

Table 36: Patient Disposition and Reason for Discontinuation - Study GO28141

Status	Vemurafenib + Placebo (N=248)	Vemurafenib + Cobimetinib (N=247)	ALL Patients (N=495)
Patients discontinued from study	67 (27.0%)	48 (19.4%)	115 (23.2%)
Death	51 (20.6%)	34 (13.8%)	85 (17.2%)
Lost To Follow-Up	3 (1.2%)	1 (0.4%)	4 (0.8%)
Withdrawal By Subject	13 (5.2%)	10 (4.0%)	23 (4.6%)
Physician Decision	0	3 (1.2%)	3 (0.6%)

Outcomes and estimation

In the primary analysis (cut-off 9 May 2014), the median duration of follow-up for all patients in the study was 7.3 months (range, 0.5–16.5 months). Patients in the cobimetinib plus vemurafenib arm had a median follow-up of 7.4 months (range, 1.4–14.7 months) while patients in the placebo plus vemurafenib arm had a median follow-up of 7.2 months (range, 0.5–16.5 months).

Primary endpoint - Progression-free survival

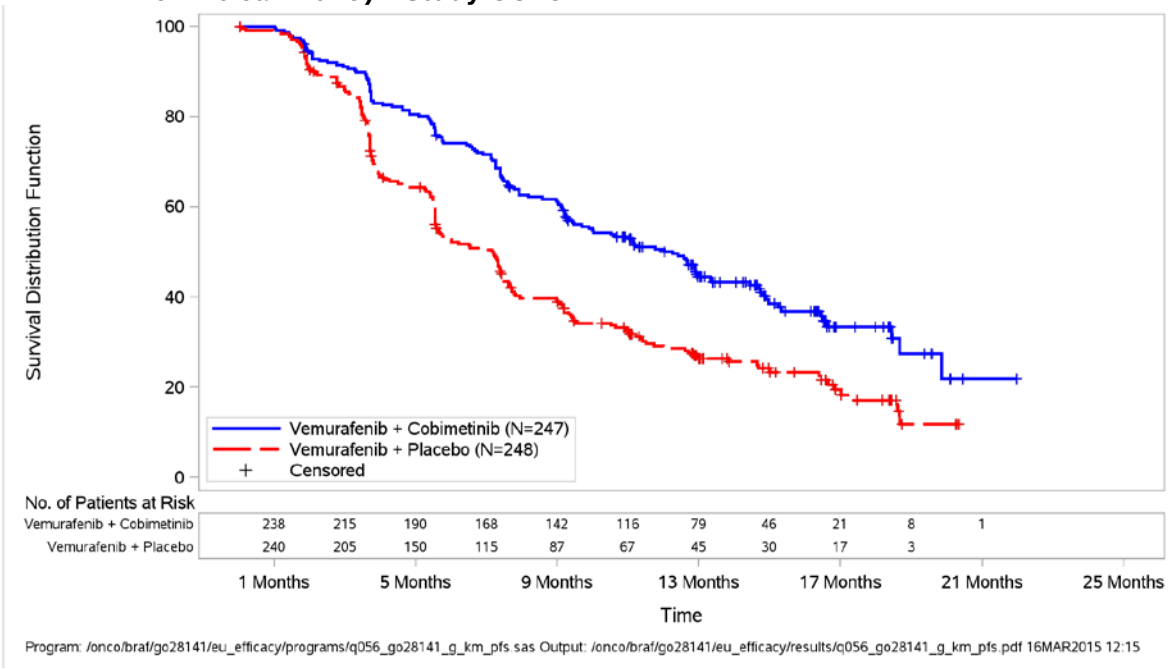
The PFS analysis (data cut-off date 16 January 2015) showed a median follow up of 14.2 months (placebo plus vemurafenib 13.6 month (0.5-24.8); cobimetinib plus vemurafenib 14.9 months (1.4-22.5). The results of the updated analysis are shown in Table 37 and Figure 10. The concordance rates (concordance of event + concordance of censored) between investigator- and IRF-based assessments was 89.0% (27.1% + 61.9%) for the cobimetinib plus vemurafenib arm and 82.6% (40.7% + 41.9%) for the placebo plus vemurafenib arm.

Table 37: Stratified Analysis of Updated Investigator-Assessed Progression-Free Survival (ITT population, cut-off 16 Jan 2015) - Study GO28141

	Vemurafenib + Placebo (N=248)	Vemurafenib + Cobimetinib (N=247)
Patients included in analysis	248 (100.0%)	247 (100.0%)
Patients with event (%)	180 (72.6%)	143 (57.9%)
Patients without event (%)	68 (27.4%)	104 (42.1%)
Time to events (Months)*		
Median (a)	7.20	12.25
95%CI for Median(b)	(5.55, 7.49)	(9.46, 13.37)
25% and 75% Percentile	3.71, 14.65	5.75, 19.84
Range	0.03 to 20.34	0.03 to 21.98
Stratified Analysis by geographic region and metastasis classification		
Hazard Ratio	0.575	
95% CI	(0.460, 0.719)	

The Kaplan-Meier plot of PFS (updated analysis) is shown in Figure 10.

Figure 10: Kaplan-Meier Plot of Updated Progression-Free Survival (ITT population, cut-off 16 Jan 2015) - Study GO28141



Secondary endpoints

An overview of the results of the efficacy secondary endpoints (cut-off 9 May 2014) is reported in Table 38.

Table 38: Summary of Secondary Efficacy Endpoints (ITT, cut-off 9 May 2014) - Study GO28141

	Placebo + Vemurafenib (n = 248)	Cobimetinib + Vemurafenib (n = 247)
PFS* (IRF)		
Median, months	6.0	11.3
95% CI	(5.6, 7.5)	(8.5, NE)
HR (95% CI)	0.60 (0.448, 0.791)	
p-value	0.0003	
Best Confirmed ORR (INV)		
n (%)	111 (44.8)	167 (67.6)
95% CI	38.5, 51.2	61.4, 73.4
Difference in ORR, % (95% CI; Hauck-Anderson)	22.9 (14.1, 31.58)	
p-value (Chi-square with Schouten Correction)	<0.0001	
Complete Response, n (%)	11 (4.4)	25 (10.1)
Partial Response, n (%)	100 (40.3)	142 (57.5)
Stable Disease, n (%)	105 (42.3)	49 (19.8)
Progressive Disease, n (%)	25 (10.1)	19 (7.7)
Non-Complete Response/ Progressive Disease	1 (0.4)	
Not Done	6 (2.4)	12 (4.9)
Duration of Response (INV)		
Patients Included in Analysis	111	167
Patients with Event, n (%)	32 (28.8)	28 (16.8)
Patients without Event, n (%)	79 (71.2)	139 (83.2)
Median Time to Event, Months	7.29	NE
95% CI	5.8, NE	9.3, NE
OS*		
Median, months	NE	NE
95% CI	NE	NE
HR (95% CI)	0.65 (0.417, 0.996)	
p-value	0.0463	

INV = per investigator assessment; IRF = per independent review facility assessment; NE = not evaluable

*Stratified analysis by geographic region and metastasis classification (disease stage)

Overall survival

Results of OS analysis (data cut-off date 16 January 2015) are shown in Figure 11 and Table 39.

Figure 11: Kaplan-Meier Plot of Updated Overall Survival (ITT population, cut-off 16 Jan 2015) - Study GO28141

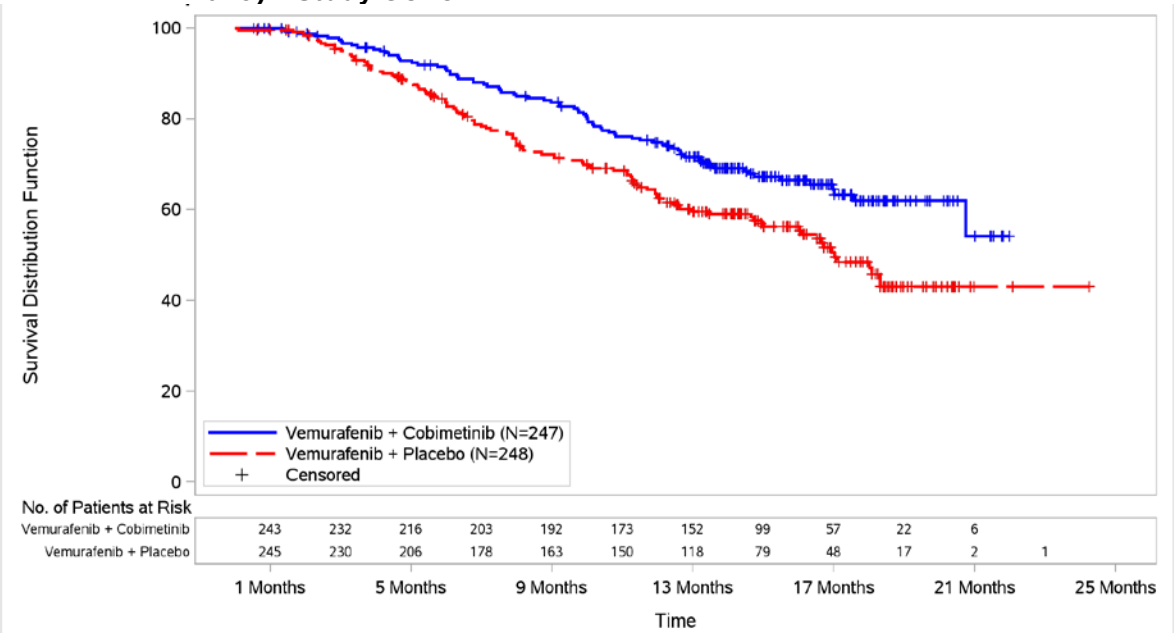


Table 39: Stratified analysis of updated overall survival (ITT population, cut-off 16 Jan 2015) - Study GO28141

	Vemurafenib + Placebo (N=248)	Vemurafenib + Cobimetinib (N=247)
Patients included in analysis	248 (100.0%)	247 (100.0%)
Patients with event (%)	109 (44.0%)	79 (32.0%)
Patients without event (%)	139 (56.0%)	168 (68.0%)
Time to events (Months)*		
Median (a)	17.02	NE
95% CI for Median(b)	(15.01, NE)	(20.73, NE)
25% and 75% Percentile	7.98, NE	11.86, NE
Range	0.10 to 24.25	0.53 to 21.98
Stratified Analysis by geographic region and metastasis classification		
Hazard Ratio	0.650	
95% CI	(0.486, 0.869)	

Objective Response Rate (ORR)

ORR was determined as the Investigator-based Best Overall Response Rate of confirmed CR or PR determined by two consecutive investigator assessments. Results are reported in in Table 40.

Table 40: Best Overall Confirmed Response rate as Determined by Investigator (ITT population, cut-off 16 Jan 2015) - Study GO28141

	Vemurafenib + Placebo (N=248)		Vemurafenib + Cobimetinib (N=247)
Patients with objective response 95% CI of objective response rate (Clopper-Pearson)	124 (50.0%) (43.61, 56.39)		172 (69.6%) (63.49, 75.31)
Difference in objective response rates 95% CI for Difference in objective response rates (Hauck-Anderson)		19.64 (10.95, 28.32)	
Complete Response (CR)	26 (10.5%)		39 (15.8%)
Partial Response (PR)	98 (39.5%)		133 (53.8%)
Stable Disease (SD)	92 (37.1%)		44 (17.8%)
Progressive Disease (PD)	25 (10.1%)		19 (7.7%)
Non CR/PD	1 (0.4%)		
Not done	6 (2.4%)		12 (4.9%)

Duration of Response (DoR)

Results in terms of DoR are summarized in Table 41.

Table 41: Objective Response Duration (by Investigator, cut-off 9 May 2014) - Study GO28141

	Vemurafenib + Placebo (N=248)	Vemurafenib + Cobimetinib (N=247)
Patients included in analysis	111 (100.0%)	167 (100.0%)
Patients with event (%)	32 (28.8%)	28 (16.8%)
Patients without event (%)	79 (71.2%)	139 (83.2%)
Time to events (Months)*		
Median (a)	7.29	NE
95% CI for Median (b)	(5.78, NE)	(9.30, NE)
25% and 75% Percentile	5.52, NE	6.41, NE
Range	1.71 to 11.04	1.28 to 11.56

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

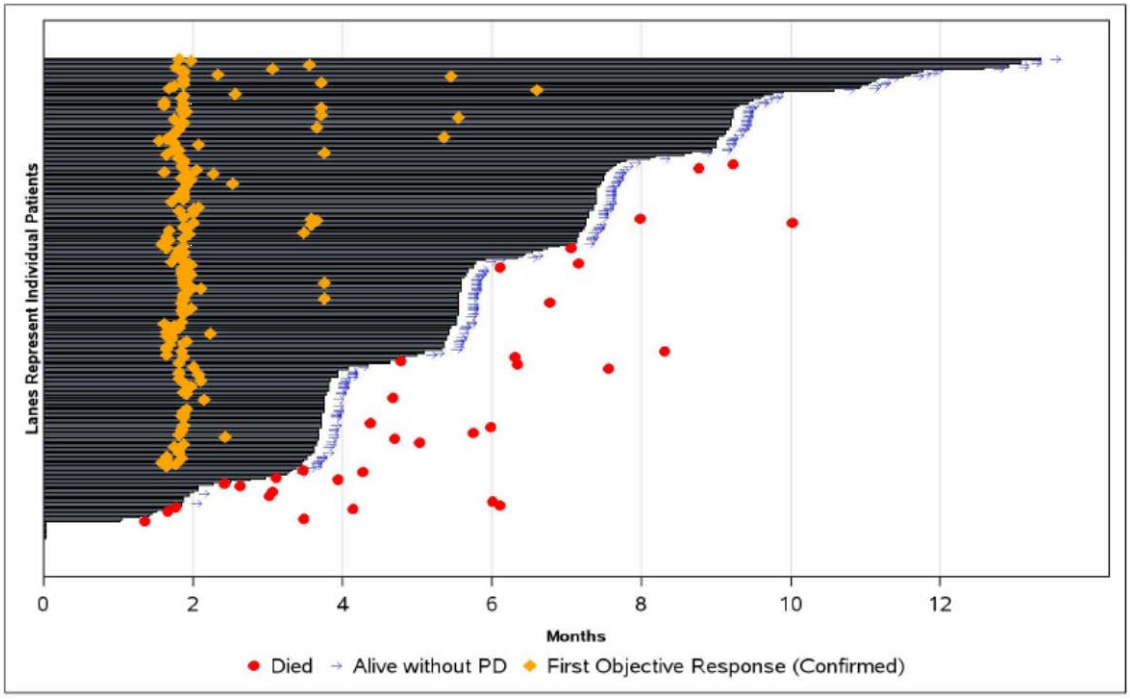
Exploratory endpoints

Time to Objective Response (TTR)

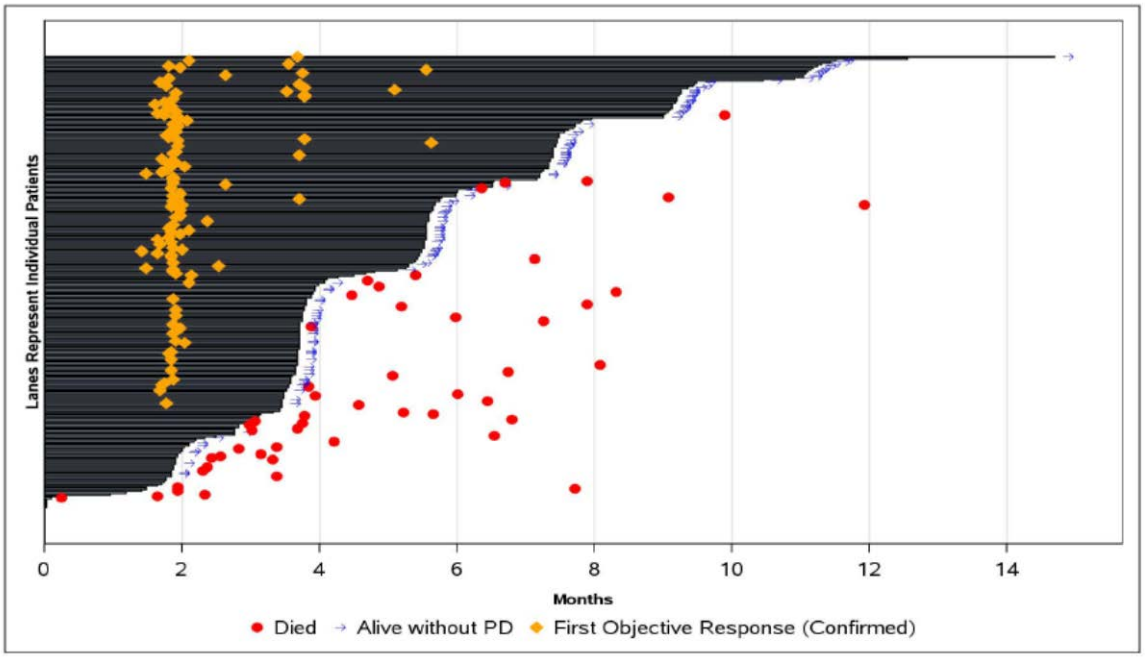
The Swimlane plots of TTR are provided in Figure 12.

Figure 12: Time to first confirmed objective response, disease progression (PD), and death in the intention-to-treat population. A) Vemurafenib + cobimetinib; B) Vemurafenib + placebo - Study GO28141

A)



B)



Data cut-off: 09 May2014

Patient-Reported Outcomes (PROs)

Global health status/health-related quality of life (HRQoL), symptom severity, and functional interference of symptoms by patient report were measured for each treatment arm using the EORTC QLQ-C30 questionnaire. The completion rate of the EORTC QLQ-C30 at baseline for both treatment arms was 96.7%. Completion rates were consistently high among all cycles for both treatment arms (≥ 88%), through the final study visit (Table 42).

Table 42: Completion of EORTC QLQ-C30 Assessment - Study GO28141

	Vemurafenib + Placebo N=209		Vemurafenib + Cobimetinib N=211	
	On Study Patients	Patients with Non-missing QLQ-C30 Score	On Study Patients	Patients with Non-missing QLQ-C30 Score
Before Disease Progression				
Baseline	202(96.7%)	202(100.0%)	205(97.2%)	204(99.5%)
Cycle 1 Day 15	200(95.7%)	182(91.0%)	203(96.2%)	179(88.2%)
Cycle 2 Day 1	195(93.3%)	177(90.8%)	198(93.8%)	188(94.9%)
Cycle 2 Day 15	191(91.4%)	168(88.0%)	189(89.6%)	178(94.2%)
Cycle 4 Day 1	156(74.6%)	140(89.7%)	174(82.5%)	163(93.7%)
Cyle 6 Day 1	106(50.7%)	99(93.4%)	139(65.9%)	128(92.1%)
Cycle 8 Day 1	54(25.8%)	49(90.7%)	86(40.8%)	79(91.9%)
Cycle 10 Day 1	26(12.4%)	25(96.2%)	44(20.9%)	43(97.7%)
Cycle 12 Day 1	13(6.2%)	12(92.3%)	16(7.6%)	16(100.0%)
Cycle 14 Day 1	5(2.4%)	4(80.0%)	4(1.9%)	4(100.0%)
Cycle 16 Day 1	2(1.0%)	1(50.0%)		
Cycle 18 Day 1	2(1.0%)	1(50.0%)		
Cycle 20 Day 1	1(0.5%)	1(100.0%)		
End of Study Treatment	58(27.8%)	58(100.0%)	43(20.4%)	42(97.7%)
Final Visit	200(95.7%)	200(100.0%)	203(96.2%)	203(100.0%)
Follow-up after Discontinuation of Treatment				
Week 4	26(12.4%)	26(100.0%)	27(12.8%)	27(100.0%)
Week 12	1(0.5%)	1(100.0%)		

Absolute scores for the EOTRTC QLQ-C30 scales and change from baseline were analysed at each assessment time point for each treatment arm. Assessments were conducted at Days 1 and 15 in Cycles 1 and 2, and every other cycle thereafter (Cycle 4, 6, 8, etc.) until patient withdrawal or end of study. Assessments up to Cycle 8 Day 1 were included in the analysis. At the time of the data cut, few patients in the study had received treatment past that time point.

An exploratory analysis was performed, in which patients were considered to have had a clinically meaningful improvement in EORTC QLQ-C30 score if they had at least a 10-point improvement in the score at one or more post-baseline assessments; this had to be an increase in the global health status and function scales and a decrease in the symptom scales[26].

Descriptive results (no formal statistical comparisons were conducted) are reported in Table 43.

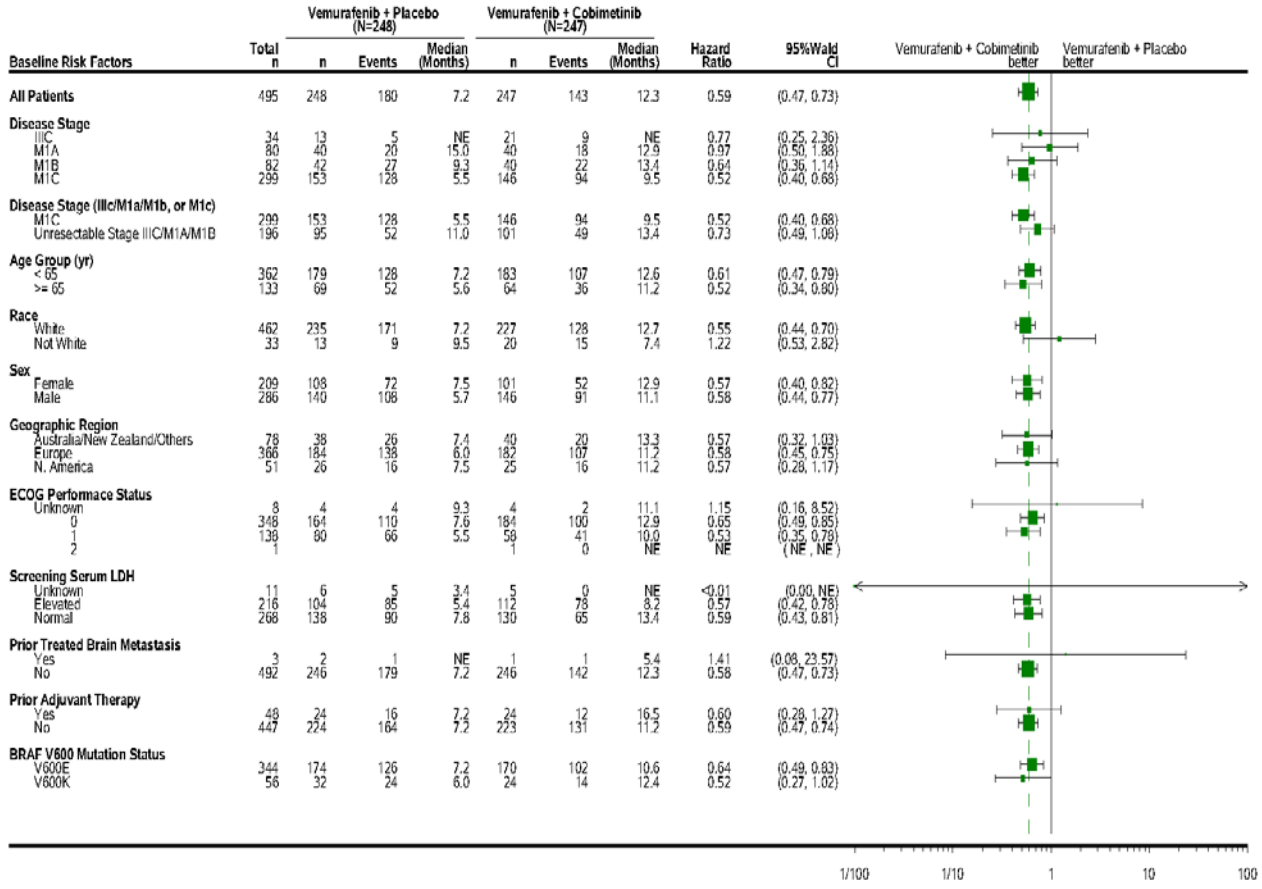
Table 43: Proportion of Patients with Clinically Significant Improvement in EORTC QLQ-C30 - Study GO28141

	Clinically Significant Improvement		
	Vemurafenib + Placebo (N=209) N(%) (95%CI)	Vemurafenib + Cobimetinib (N=211) N(%) (95%CI)	Difference in Treatment CS Proportions % (95%CI)
Global Health Status	76 (37.6%) (30.92, 44.37)	74 (36.3%) (29.68, 42.94)	-1.35 (-10.74, 8.04)
Functioning Scales			
Physical	54 (26.7%) (20.77, 33.28)	65 (31.9%) (25.53, 38.62)	5.13 (-3.71, 13.97)
Role	62 (30.7%) (24.65, 37.33)	70 (34.3%) (27.83, 41.01)	3.62 (-5.48, 12.73)
Emotional	104 (51.5%) (44.37, 58.56)	111 (54.4%) (47.54, 61.38)	2.93 (-6.78, 12.63)
Cognitive	60 (29.7%) (23.49, 36.14)	68 (33.3%) (27.05, 40.05)	3.63 (-5.40, 12.66)
Social	66 (32.7%) (26.26, 39.50)	88 (43.1%) (36.48, 50.06)	10.46 (1.08, 19.85)
Symptom Scales			
Fatigue	90 (44.6%) (37.76, 51.65)	109 (53.4%) (46.50, 60.43)	8.88 (-0.81, 18.56)
Nausea and Vomiting	45 (22.3%) (16.94, 28.58)	57 (27.9%) (21.90, 34.35)	5.66 (-2.75, 14.08)
Pain	90 (44.6%) (37.76, 51.65)	105 (51.5%) (44.41, 58.51)	6.92 (-2.78, 16.61)
Dyspnoea	49 (24.3%) (18.52, 30.45)	55 (27.0%) (21.16, 33.41)	2.70 (-5.78, 11.19)
Insomnia	77 (38.1%) (31.55, 44.86)	110 (53.9%) (47.02, 60.91)	15.80 (6.23, 25.38)
Appetite Loss	57 (28.2%) (22.13, 34.71)	69 (33.8%) (27.57, 40.53)	5.61 (-3.38, 14.59)
Constipation	37 (18.3%) (13.49, 24.03)	47 (23.0%) (17.45, 29.21)	4.72 (-3.14, 12.59)
Diarrhoea	26 (12.9%) (8.59, 18.07)	29 (14.2%) (9.73, 19.66)	1.34 (-5.31, 8.00)

Ancillary analyses

The PFS results in pre-specified subgroups analysis are reported in Figure 13, respectively.

Figure 13: Forest Plot for Hazard Ratios of updated Progression-Free Survival Subgroup Analyses (ITT population, cut-off 16 Jan 2015) - Study GO28141



Progression-Free Survival by Independent Review Facility (IRF)

Results in terms of PFS by IRF (cut-off 9 May 2014) are shown in Figure 14 and Table 44.

Figure 14: Kaplan-Meier Plot for Progression-Free Survival by IRF (ITT population, cut-off 9 May 2014) - Study GO28141

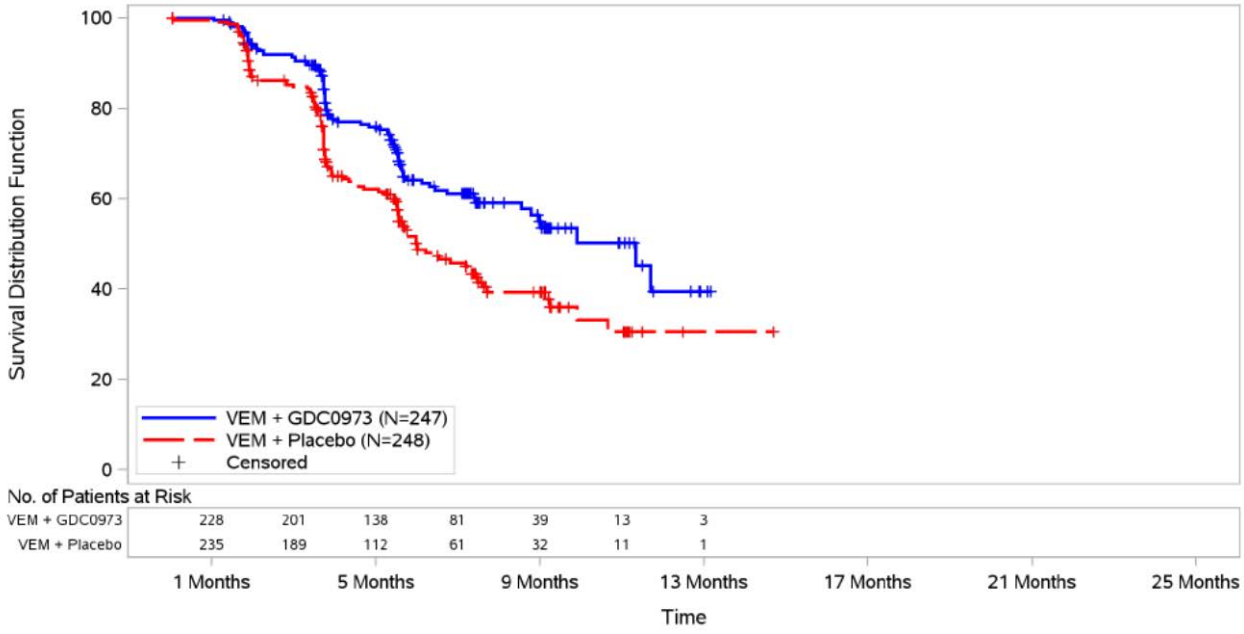


Table 44: Progression-Free Survival Analysis by IRF with/without Stratifications (ITT population, cut-off 9 May 2014) - Study GO28141

	Vemurafenib + Placebo (N=248)	Vemurafenib + Cobimetinib (N=247)
Patients included in analysis	248 (100.0%)	247 (100.0%)
Patients with event (%)	117 (47.2%)	82 (33.2%)
Patients without event (%)	131 (52.8%)	165 (66.8%)
Time to events (Months)*		
Median (a)	6.01	11.33
95% CI for Median(b)	(5.55, 7.49)	(8.54, NE)
25% and 75% Percentile	3.71, NE	5.29, NE
Range	0.03 to 14.69	0.03 to 13.17
Stratified Analysis by geographic region and metastasis classification		
p-value (log-rank)	0.0003	
Hazard Ratio	0.595	
95% CI	(0.448, 0.791)	
Unstratified Analysis		
p-value (log-rank)	0.0006	
Hazard Ratio	0.613	
95% CI	(0.462, 0.813)	

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

Summary of main study

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

Table 45: Summary of efficacy for phase III trial GO28141

Title: A Phase III, Double-Blind, Placebo-controlled Study of Vemurafenib Versus Vemurafenib plus GDC-0973 (cobimetinib) in Previously Untreated BRAF V600-Mutation Positive Patients with Unresectable Locally Advanced or Metastatic melanoma			
Study identifier	GO28141, NCT01689519, 2012-003008-11		
Design	global, multicenter, randomised, double-blind, placebo-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Until disease progression (by investigator's assessment), death, development of unacceptable toxicity, or withdrawal of consent not applicable not applicable
Hypothesis	Superiority		
Treatments groups	cobimetinib+vemurafenib		cobimetinib 60 mg QD, days 1-21 vemurafenib 960 mg BID, days 1-28 N=247
	placebo+vemurafenib		placebo QD, days 1-21 vemurafenib 960 mg BID, days 1-28 N=248
Endpoints and definitions	Primary endpoint	Progression Free Survival by investigator (PFS)	Time from randomization to the first occurrence of disease progression, as determined by the investigator using RECIST v1.1, or death from any cause, whichever comes first.
	Secondary endpoint	PFS by independent review	Time from randomization to the first occurrence of disease progression, as determined by independent review using RECIST v1.1, or death from any cause, whichever comes first.
	Secondary endpoint	Overall survival (OS)	Time from randomization to death from any cause
	Secondary endpoint	Objective response rate (ORR)	Proportion of patients who had complete or partial response as determined by investigator using RECIST 1.1
	Secondary endpoint	Duration of response (DOR)	Time from first occurrence of documented objective response until the time of disease progression, as determined by investigator using RECIST 1.1
Database lock	09 May 2014		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat 09 May 2014		

Descriptive statistics and estimate variability	Treatment group	Cobimetinib+vemurafenib	Placebo+vemurafenib
	Number of subject	247	248
	PFS by investigator (median, in months)	9.9	6.2
	95% CI	9.0, NE	5.6, 7.4
	PFS by independent review (median, in months)	11.3	6.0
	95% CI	8.5, NE	56, 7.5
	OS (median, in months)	NE	NE
	95% CI	NE	NE
	ORR by investigator (N (%))	167(67.6)	111 (44.8)
	95% CI	61.4, 73.4	38.5, 51.2
	DOR by investigator (median, in months)	NE	7.3
	95% CI	9.3, NE	5.8, NE

Effect estimate per comparison	Primary endpoint PFS by investigator	Comparison groups	Cobimetinib+vemurafenib vs placebo+vemurafenib
		HR (stratified)	0.51
		95% CI	0.39, 0.68
		P-value	<0.001
	Secondary endpoint PFS by independent review	Comparison groups	Cobimetinib+vemurafenib vs placebo+vemurafenib
		HR (stratified)	0.60
		95% CI	0.45, 0.79
		P-value	0.0003
	Secondary endpoint OS	Comparison groups	Cobimetinib+vemurafenib vs placebo+vemurafenib
		HR (stratified)	0.65
		95% CI	0.42, 1.00
		P-value	0.0463
	Secondary endpoint ORR	Comparison groups	Cobimetinib+vemurafenib vs placebo+vemurafenib
		Difference in ORR (%)	22.9
		95% CI	14.1, 31.58

		P-value	<0.0001
Notes	This summary represents topline efficacy results from the primary analysis for the Phase 3 study GO28141. Detailed analysis of the efficacy data, and results from other secondary and exploratory objectives, are provided in the report as updated analyses (data cut-off date: 16 January 2015).		

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

The applicant did not submit analyses across trials.

Clinical studies in special populations

The number of patients by age group are shown in Table 46. The denominator is 745 patients, which includes all patients in studies GO28141 (495 enrolled, 493 treated), NO25395 (131 enrolled and treated) and MEK4592g (119 enrolled, 115 treated).

Table 46: Clinical Studies by Age Groups

	Age 65-74 n=145 (19.5%)	Age 75-84 n=56 (7.5%)	Age 85+ n=6 (0.8%)
Controlled Trials	90 (12.1%)	38 (5.1%)	5 (0.7%)
GO28141	90 (12.1%)	38 (5.1%)	5 (0.7%)
Cobimetinib plus Vemurafenib	44 (5.9%)	16 (2.1%)	4 (0.5%)
Placebo plus Vemurafenib	46 (6.2%)	22 (3.0%)	1 (0.1%)
Non Controlled trials	55 (7.4%)	18 (2.4%)	1 (0.1%)
NO25395	27 (3.6%)	4 (0.5%)	1 (0.1%)
MEK4592g	28 (3.8%)	14 (1.9%)	0

Supportive studies

Study NO25395 (BRIM7)

Study NO25395 was a Phase Ib, open label, dose-escalation study evaluating the safety, tolerability and pharmacokinetics of vemurafenib in combination with GDC-0973 (cobimetinib) when administered in BRAFV600E mutation–positive patients previously treated (but without prior exposure to BRAF or MEK inhibitor therapy) or previously untreated for locally advanced/unresectable or metastatic melanoma or those who have progressed after treatment with vemurafenib.

Study NO25395 (BRIM7), was an open-label, multicenter, Phase 1b study designed to assess the safety, tolerability, PK, and efficacy of cobimetinib in combination with vemurafenib, and to determine the recommended cobimetinib dose and schedule to be used in Phase 3. The study was conducted at 9 sites in the US and 1 site in Australia.

The following patient populations with BRAF V600E mutation-positive (as detected by the cobas 4800 BRAF V600 Mutation Test), locally-advanced, and unresectable or metastatic melanoma were eligible for Study NO25395 (BRIM7):

1. BRAF inhibitor (BRAFi)-naïve patients, either:
    a) Previously untreated patients
    b) Previously treated patients who were naïve to BRAF or MEK inhibitor therapy.

2. Patients who progressed on vemurafenib monotherapy immediately prior to enrolment on Study NO25395 (BRIM7).

Key inclusion criteria were:
1. Patients with the BRAF mutation detected by the cobas® 4800 BRAF V600 mutation test in melanoma tumour tissue.
2. Patients with histologically confirmed melanoma, either unresectable Stage IIIc or Stage IV metastatic melanoma, as defined by American Joint Committee on Cancer (AJCC)
3. Measurable disease per RECIST v1.1
4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1.

There were two stages: a dose-escalation stage and a cohort expansion stage.

The dose-escalation stage consisted of 9 dose-escalation cohorts of 3 to 6 patients. Dose-escalation proceeded in standard 3+3 design. Please refer to section 3.3 'Dose-response studies' for the study outcomes.

Table 47: Cohort Assignment of Patients in Study NO25395

Cohort	Cobimetinib Dose (mg) and Schedule	Vemurafenib Dose (mg)	BRAFi-Naïve Patients n	Vemurafenib-PD Patients n
Dose-Escalation Stage[a]				
1	60 (14/14)	720	-	5
2	80 (14/14)	720	-	4
2A	100 (14/14)	720	2	2
3	60 (14/14)	960	-	3
4	80 (14/14)	960	3	2
1A	60 (21/7)	720	2	6
1B	60 (21/7)	960	19	8
1C	60 (28/0)	720	1	2
1D	60 (28/0)	960	4	-
Cobimetinib Monotherapy	100 (14/14) 60 (21/7)	N/A N/A	- -	1 1
Cohort-Expansion Stage				
1A	60 (21/7)	720	12	15
1B	60 (21/7)	960	20	19

BRAFi-naïve = BRAF inhibitor-naïve; n = number of patients;
vemurafenib-PD = vemurafenib-progressive disease
14/14 schedule: once daily on Days 1 to 14, followed by 14 days off on Days 15 to 28
21/7 schedule: once daily on Days 1 to 21, followed by 7 days off on Days 22 to 28
28/0 schedule: once daily on Days 1 to 28
[a] Patients accrued in the dose-escalation stage comprised of vemurafenib-PD patients and BRAFi-naïve patients.

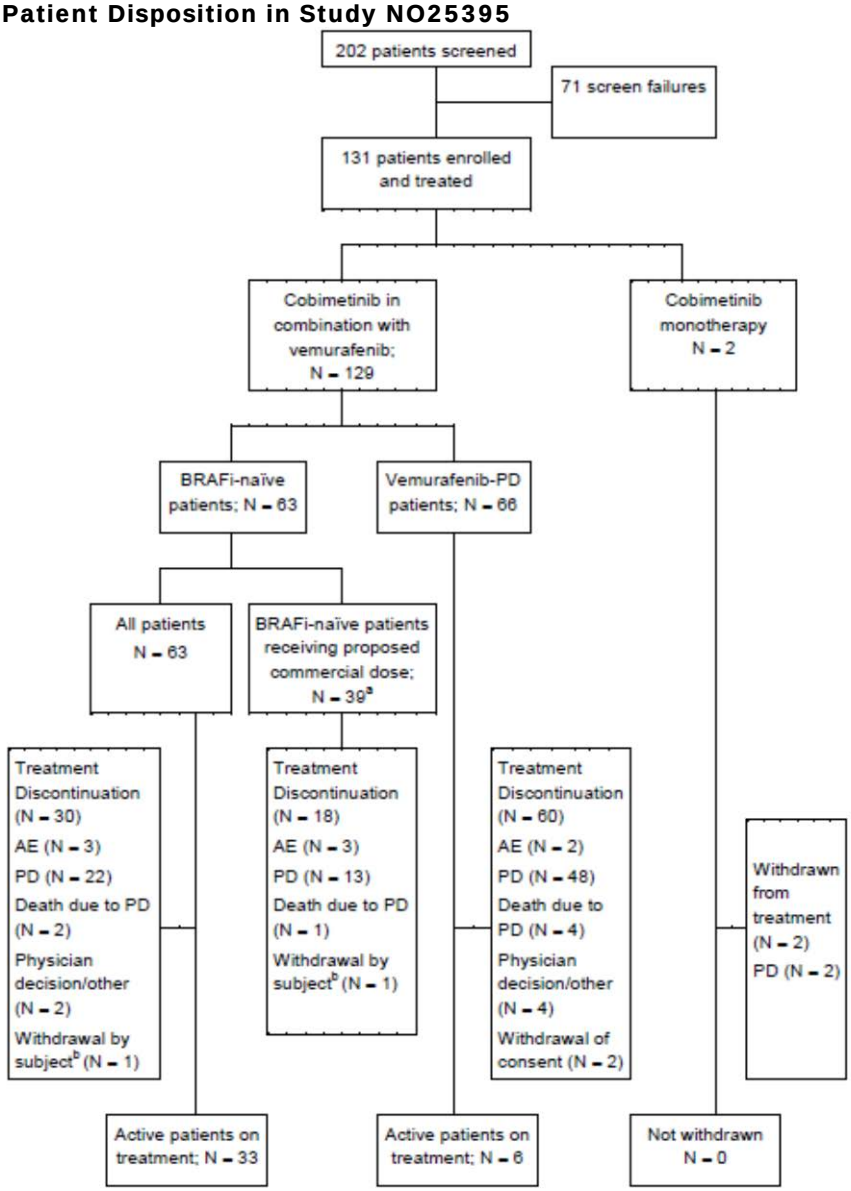
In the cohort expansion stage, 2 selected cohorts were expanded after being declared safe and tolerable in the dose-escalation stage. Twenty BRAFi-naïve patients and 19 vemurafenib-PD patients, were accrued into the expansion cohort corresponding to the proposed commercial dose/schedule that were chosen for the phase III study. In the dose-escalation 1B stage, 19 BRAFi-naive AND 8 vemurafenib-PD patients were exposed to these dose and schedule. Expansion cohorts allowed for the establishment of the safety profile, PK and efficacy of the combination in relatively large and homogenous patient populations with advanced BRAF-mutated melanoma receiving a uniform dose and schedule of the combination.

Results

Patient disposition

The first patient was treated on 17 February 2011, and a data cutoff date of 01 October 2013 was used for analyses.

Figure 15: Patient Disposition in Study NO25395



AE = adverse event; BRAFi-naïve = BRAF inhibitor-naïve; PD = progressive disease

[a] These patients are a subset of the BRAFi-naïve patients (N = 63)

[b] Patient 1107 refused treatment and withdrew from the study on 16 April 2013 (Day 147). The best response for Patient 1107 was stable disease at the last study assessment (on Cycle 5, Day 1).

Demographics and baseline characteristics

Table 48 summarises the key demographic and baseline characteristics of all patients (n=129) who received both cobimetinib and vemurafenib.

Table 48: Summary of Key Demographic and Baseline Characteristics of all Patients treated with Cobimetinib in Combination with Vemurafenib in Study NO25395

	BRAFi-Naïve Patients		Vemurafenib-PD Patients
	All Doses (N=63)	960 mg Vem + 60 mg Cobi 21/7 (N=39)[a]	All Doses (N=66)
Age (years)			
Mean (SD)	54.0 (13.0)	54.0 (14.6)	53.0 (14.8)
Median	56.0	56.0	53.0
Range	21 – 74	21 – 74	19 – 88
Sex			
Male	35 (55.6%)	19 (48.7%)	42 (63.6%)
Female	28 (44.4%)	20 (51.3%)	24 (36.4%)
Race			
White	62 (98.4%)	38 (97.4%)	63 (95.5%)
Other	0	0	3 (4.5%)
Unknown	1 (1.6%)	1 (2.6%)	0
Metastatic Melanoma Stage at Enrollment			
Unresectable Stage IIIC	7 (11.1%)	3 (7.7%)	3 (4.5%)
M1a	3 (4.8%)	2 (5.1%)	4 (6.1%)
M1b	9 (14.3%)	4 (10.3%)	5 (7.6%)
M1c	44 (69.8%)	30 (76.9%)	54 (81.8%)
Screening Serum Lactate Dehydrogenase			
Lactate dehydrogenase normal	34 (54.0.0%)	20 (51.3%)	24 (38.1%)[b]
Lactate dehydrogenase Elevated	29 (46.0%)	19 (48.7%)	39 (61.9%)
Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline			
0	41 (65.1%)	28 (71.8%)	23 (34.8%)
1	22 (34.9%)	11 (28.2%)	43 (65.2%)
Treatment Status			
Previously untreated	43 (68.3%)	27 (69.2%)	0
Previously treated but without prior exposure to any BRAF inhibitor or MEK inhibitor therapy	20 (31.7%)	12 (30.8%)	0
Vemurafenib-PD	0	0	66 (100.0%)

BRAFi-naïve = BRAF inhibitor-naïve; N=total number of patients; SD=standard deviation; vemurafenib-PD = vemurafenib-progressive disease

[a] These patients are a subset of the BRAFi-naïve patients (N = 63)

[b] LDH data available for 63 patients.

Duration of Follow-up

For the vemurafenib-PD patients, the median duration of follow-up was 6.6 months. For the BRAFi-naïve patients, the median duration of follow-up was 11.0 months.

Prior anti-cancer treatments

The table below summarise previous anti-cancer treatments in BRAFi-naïve patients, vemurafenib-PD patients, and all patients in the study who received cobimetinib in combination with vemurafenib.

Table 49: Prior Anti-Cancer Treatment - Study NO25395

	Vemurafenib-PD patients (n=66)	BRAFi-naïve patients (n=63)	All patients (n=129)
Prior cancer treatment			
n	66	63	129
Yes	66 (100%)	62 (98.4%)	128 (99.2%)
Prior cancer-related surgery			
n	66	63	129
Yes	63 (95.5%)	61 (96.8%)	124 (96.1%)
No	3 (4.5%)	2 (3.2%)	5 (3.9%)
Prior radiotherapy			
n	66	63	129
Yes	26 (39.4%)	13 (20.6%)	39 (30.2%)
No	40 (60.6%)	50 (79.4%)	90 (69.8%)
Prior systemic therapy			
n	66	63	129
Yes	66 (100%)	19 (30.2%)	85 (65.9%)
No	(0.0%)	44 (69.8%)	44 (34.1%)

Efficacy outcomes

The efficacy data presented include objective response rate (ORR), duration of response (DOR) and progression-free survival (PFS), on the basis of investigator assessment using RECIST 1.1, and overall survival (OS). All efficacy data analyses used the treated population, defined as all patients who received at least one of study drug.

The efficacy data have been pooled across dose/regimen cohorts from the dose-escalation and cohort-expansion stages and analysed separately for BRAFi-naïve and vemurafenib-PD patients who received both cobimetinib and vemurafenib.

A summary of the main efficacy results is provided in the table below.

Table 50: Summary of Efficacy Parameters - Study NO25395

	BRAFi–Naïve Patients		Vemurafenib-PD Patients
	All Doses (N = 63)	960 mg Vem + 60 mg Cobi 21/7 (N=39)[a]	All Doses (N=66)
Objective response rate[b]			
Patients with objective response, n (%)	55 (87.3%)	33 (84.6%)	10 (15.2%)
95% CI for objective response rate	(76.7%, 94.4%)	(69.9%, 93.1%)	(7.5%, 25.5%)
Best Overall Response			
Complete response, n (%)	6 (9.5%)	4 (10.3%)	0
Partial response, n (%)	49 (77.8%)	29 (74.4%)	10 (15.2%)
Stable disease, n (%)	6 (9.5%)	4 (10.3%)	28 (42.4%)
Progressive disease, n (%)	2 (3.2%)	2 (5.1%)	24 (36.4%)
Unable to assess, n (%)	0	0	2[c] (3.0%)
Not done, n (%)	0	0	2 (3.0%)
Duration of response			
Patients with objective response, n	55	33	10
Median duration of response (months)	12.5	11.3	6.7
95% CI for median	9.7–NE	8.8 – 15.2	4.9–NE
PFS			
Patients with event, n (%)	33 (52.4%)	22 (56.4%)	58 (87.9%)
Time to event (months)			
Median	13.7	12.7	2.8
95% CI for median	10.1–17.5	9.7 – 16.6	2.6–3.5
OS			
Patients with event, n (%)	12 (19.0%)	7 (17.9%)	45 (68.2%)
Estimate of 1-year survival rate	82.8%	82.4%	31.9%
95% CI for 1-year survival rate	(72.9, 92.6%)	(69.4, 95.4%)	(19.4, 44.6%)

CI=confidence interval; N=total number of patients; n=number of patients included in the analysis; NE=not estimable; PFS=progression-free survival

[a] These patients are a subset of the BRAFi-naïve patients (N = 63)

[b] Assessed and confirmed by RECIST v1.1.

[c] Unable to assess denotes patients who had a post-baseline tumor assessment which was performed prior to the minimum required interval of 6 weeks for response assessment.

The Kaplan-Meier PFS curves for BRAFi-naïve and vemurafenib-PD patients are depicted in Figure 16 and Figure 17, respectively.

Figure 16: Kaplan-Meier plot of PFS in BRAFi-naïve patients - NO25395

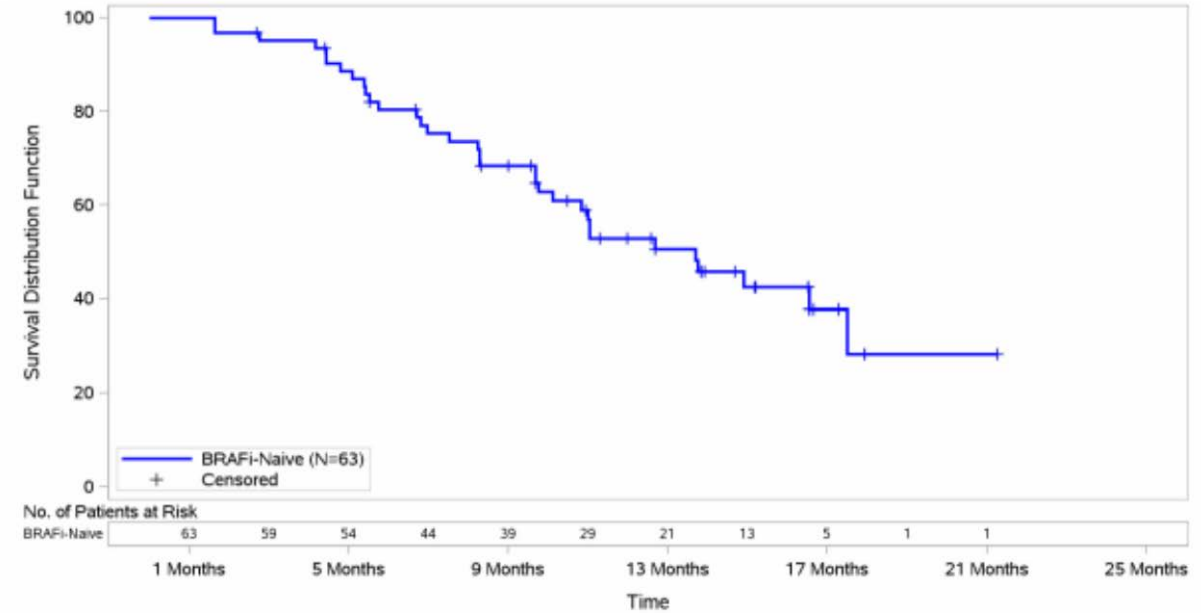
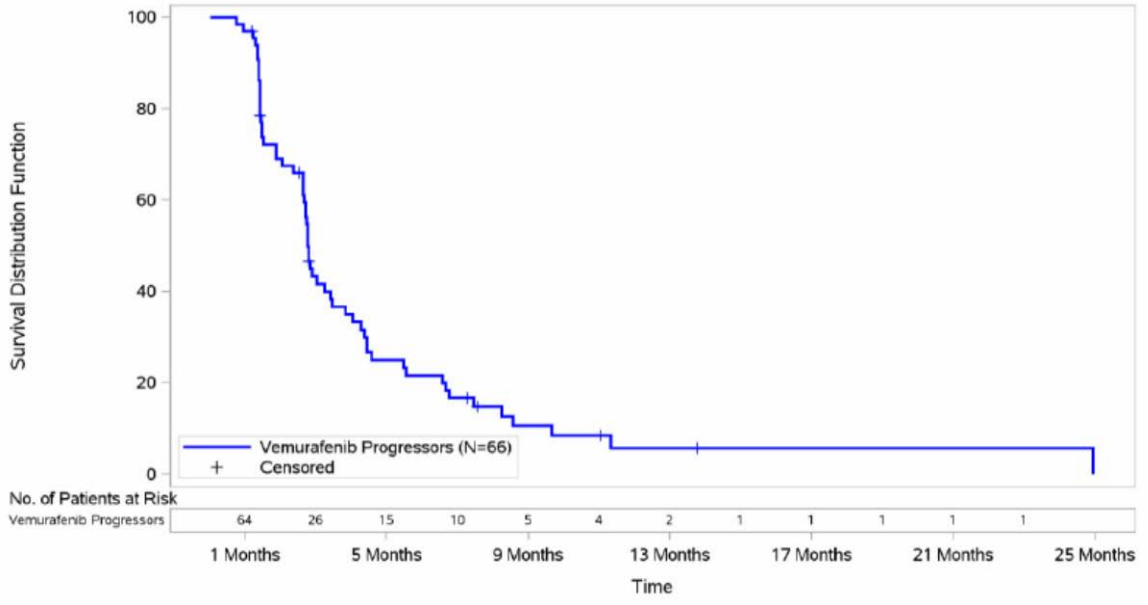


Figure 17: Kaplan-Meier plot of PFS in vemurafenib-PD patients - Study NO25395



PD = progressive disease

The Kaplan-Meier OS curves for BRAFi-naïve and vemurafenib-PD patients are depicted in Figure 18 and Figure 19, respectively.

Figure 18: Kaplan-Meier plot of OS in BRAFi-naïve patients - Study NO25395

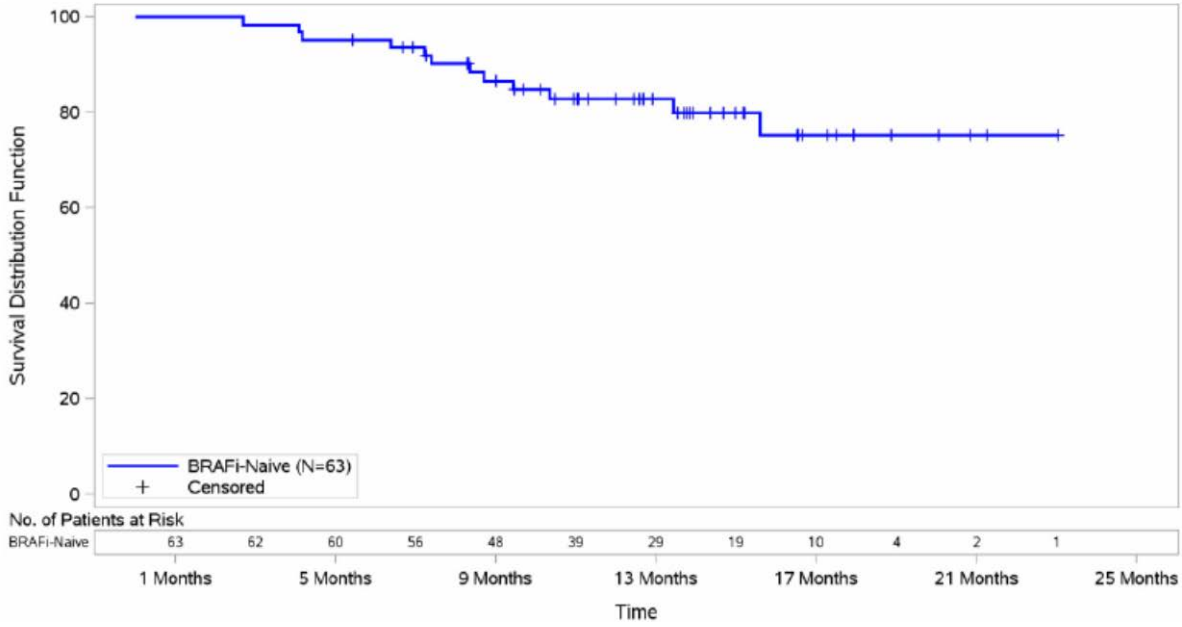
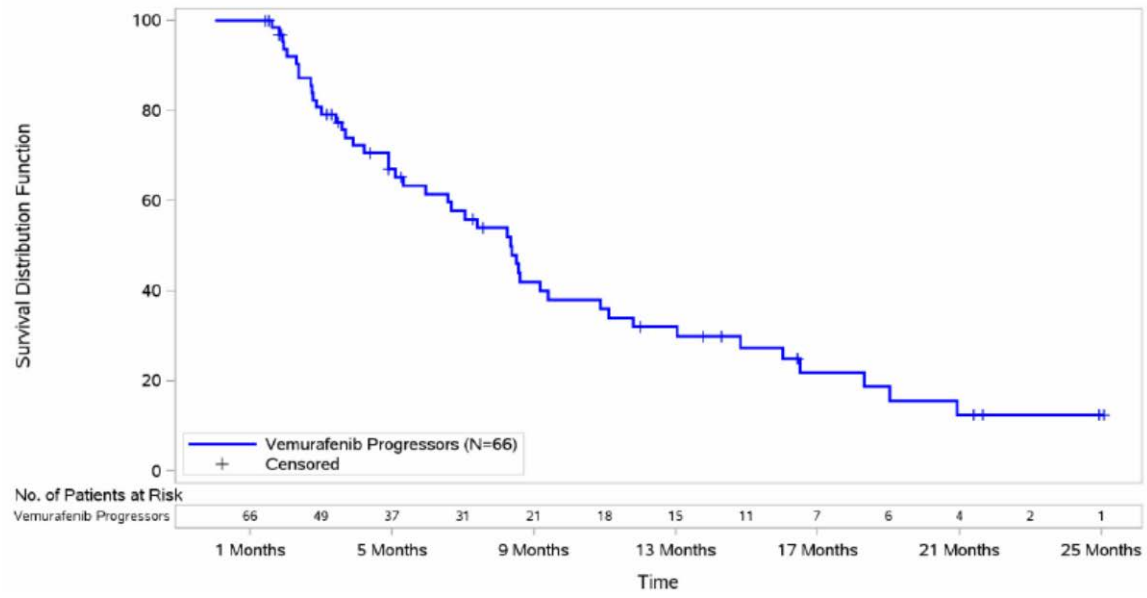


Figure 19: Kaplan-Meier plot of OS in vemurafenib-PD patients - Study NO25395



PD = progressive disease

MEK4592g - monotherapy

Methods

This was a Phase I, non-randomised, open-label, safety and pharmacokinetic (PK) dose-escalation study. The study consisted of 4 treatment stages listed below. A conventional 3+3 design was used for Stage I and IA, with each cohort consisting of 3 to 6 subjects.

Stage I: Dose-escalation cohorts were treated on a 21-days-on, 7-days-off (21/7) schedule to determine the MTD.

Stage IA: Dose-escalation cohorts, starting at the MTD of the 21-days-on, 7-days-off (21/7) schedule, were treated on a 14-days-on, 14-days-off (14/14) schedule to determine the MTD on an alternate dosing regimen.

Stage II: Expansion cohort with the MTD determined in Stage I in approximately 20 patients with FDG-PET-avid tumours harbouring a BRAF, NRAS, or KRAS mutation and with FDG-PET-avid disease.

Stage IIA: Expansion cohort with the MTD determined in Stage IA in approximately 20 patients with FDG-PET-avid tumours harbouring a BRAF, NRAS, or KRAS mutation.

Information collected during the first 28 day cycle of treatment period was used to determine the MTD and dose-limiting toxicities (DLTs). Confirmation of objective responses was applied.

Number of Patients (Planned and Analysed)

Approximately 90 patients were planned for enrolment. A total of 99 patients were enrolled, 97 of whom received at least 1 dose of study drug and are included in the analyses.

Of the 146 patients screened, 47 patients were screen failures and 99 patients were enrolled in the study: 36 patients in Stage I, 20 patients in Stage IA, 21 patients in Stage II, 22 patients in Stage IIA.

Main eligibility criteria

Stage I: The patient had a histologically confirmed solid tumour that was metastatic or unresectable, and for which standard curative or palliative measures did not exist or were no longer effective, and there were no therapies known to prolong survival. The patient had disease that was assessable by tumour marker, physical, or radiologic means.

Stages IA, II, IIA: As above + No prior GDC-0973/XL518 (cobimetinib) + measureable disease (by RECIST criteria).

Stages II and IIA: As above + The patient's current cancer, for which he or she was enrolled in this study, must have harboured a known BRAF, NRAS, or KRAS mutation + Patients must have had FDG-PET-avid disease: At least 1 target lesion on computed tomography (CT) scans must have also been a FDG-PET-avid region of interest.

Treatments

The study drug was supplied as GDC-0973/XL518 drug substance powder in an amber glass bottle (powder-in-bottle [PIB]) and as a powder-in-capsule. GDC-0973/XL518 was administered orally, either via solution or capsule, once daily for Days 1-21 (Stages I and II) or Days 1-14 (Stages IA and IIA) of each 28-day cycle.

The dose cohorts ranged between 0.05 mg/kg bodyweight– 0.20 mg/kg, and 20mg – 80 mg in the 21/7 day dosing regimen, and 60-125 mg in the 14/14 day regimen. The solution was given at the doses: 0.05, 0.1, and 0.2 mg/kg.

Results

Baseline characteristics: 11 /97 (11%) patients in Study MEK4592g had melanoma. In addition there was 1 patient with ocular melanoma and 1 with choroidal mixed-type melanoma, categorised as tumour type "other". The most common primary cancer sites in this study were colorectal (33 patients), other (26 patients), melanoma (11 patients), and colon (6 patients). Four of the 11

melanoma patients were included in the dose regimen 60 mg 21/7, and 7 in cohorts with 100 mg 14/14.

DLT: Six patients experienced a dose-limiting toxicity, including 2 patients with Grade 3 rash (21/7 regimen at 60 mg and 80mg, respectively), 1 patient with Grade 4 hepatic encephalopathy (40 mg 21/7), Grade 3 acneiform dermatitis (60 mg 21/7), Grade 3 diarrhoea (80 mg 21/7), and 1 patient with Grade 3 blurred vision due to serous macular detachment (125 mg 14/14 – this dose was determined to exceed the MTD)

Table 51 : Dose-limiting Toxicities in Phase I study MEK4592g

Patient ID	Preferred Term	Start/Stop Date	NCI CTCAE Grade	SAE	Relationship	Action Taken	Outcome
Cohort 06: 40 mg							
0011040601	Hepatic encephalopathy	25 April 2008/ 8 May 2008	4	Yes	Probably	Dose withdrawn	Resolved
Cohort 07: 60 mg							
0011030701	Dermatitis acneiform	23 August 2008/ongoing	3	No	Probably	Dose interrupted	Not resolved
Cohort 08: 80 mg							
0011040803	Rash	26 December 2008/ 18 January 2009	3	No	Probably	Dose decreased	Resolved with sequelae
0011040805	Diarrhea	23 February 2009/ 25 February 2009	3 [a]	Yes	Probably	Dose withdrawn	Resolved
Cohort 04A: 125 mg							
0011040427	Vision blurred	27 January 2010/ 31 January 2010	3	Yes	Probably	Dose held	NR
0011050451	Rash	13 December 2009/ 16 December 2009	3	No	Probably	Dose decreased	NR

NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; NR=not reported; SAE=serious adverse event.

Notes: Cohorts 06, 07, and 08 (maximum tolerated dose expansion) are associated with the 21/7 dosing regimen. Cohort 04A (maximum tolerated dose expansion) is associated with the 14/14 dosing regimen.

Event coding is from the Medical Dictionary for Regulatory Activities (version 15.0). At each level of patient summarization, a patient was counted once if the patient reported 1 or more events.

a. Patient 1040805 had Grade 3 diarrhea that was a dose-limiting toxicity but erroneously listed as Grade 2. This should have been changed with data cleaning.

MTD: The MTD for the 21/7 QD schedule was found to be 60 mg and the MTD for the 14/14 QD schedule was found to be 100 mg.

QTc: Overall, during Stages IA, II, and IIA, 5 patients (8.2%) and 2 patients (3.3%) experienced QTcB and QTcF prolongation, respectively; all these patients were in Cohort 03A (100 mg, escalation cohort, 14/14 schedule) and Cohort 30 (100 mg, expansion cohort, 14/14 schedule).

Tumour activity: Overall, 6 patients with melanoma had a confirmed partial response, 28 patients had stable disease, and 40 patients had disease progression (Table 52). Three patients, who were ongoing in the study at the time of database lock, were responding to the study drug: 1 patient with prolonged stable disease and 2 patients with partial responses.

Table 52: Tumour Response – Study MEK4592g

Response	No. (%) of Patients				
	Cohort 01 0.05 mg/kg (N=4)	Cohort 02 0.10 mg/kg (N=3)	Cohort 03 0.20 mg/kg (N=3)	Cohort 04 10 mg (N=3)	Cohort 05 20 mg (N=3)
Confirmed partial response	0	0	0	0	0
Stable disease	1 (25.0)	2 (66.7)	1 (33.3)	2 (66.7)	0
Disease progression	1 (25.0)	1 (33.3)	1 (33.3)	1 (33.3)	2 (66.7)
Objective response rate	0	0	0	0	0
95% confidence interval [a]	NA	NA	NA	NA	NA
Disease stabilization rate	1 (25.0)	2 (66.7)	1 (33.3)	2 (66.7)	0
95% confidence interval [a]	0.6, 80.6	9.4, 99.2	0.8, 90.6	9.4, 99.2	NA

Response	No. (%) of Patients				
	Cohort 06 40 mg (N=6)	Cohort 07 60 mg (N=7)	Cohort 08 80 mg (N=7)	Cohort 20 60 mg (N=20)	Cohort 01A 60 mg (N=3)
Confirmed partial response	0	0	0	3 (15.0)	0
Stable disease	4 (66.7)	2 (28.6)	1 (14.3)	3 (15.0)	2 (66.7)
Disease progression	1 (16.7)	3 (42.9)	4 (57.1)	10 (50.0)	1 (33.3)
Objective response rate	0	0	0	3 (15.0)	0
95% confidence interval [a]	NA	NA	NA	(3.2, 37.9)	NA
Disease stabilization rate	4 (66.7)	2 (28.6)	1 (14.3)	6 (30.0)	2 (66.7)
95% confidence interval [a]	22.3, 95.7	3.7, 71.0	0.4, 57.9	11.9, 54.3	9.4, 99.2

Response	No. (%) of Patients				
	Cohort 02A 80 mg (N=3)	Cohort 03A 100 mg (N=8)	Cohort 04A 125 mg (N=6)	Cohort 30 100 mg (N=21)	Total (N=97)
Confirmed partial response	0	1 (12.5)	0	2 (9.5)	6 (6.2)
Stable disease	0	2 (25.0)	1 (16.7)	7 (33.3)	28 (28.9)
Disease progression	2 (66.7)	3 (37.5)	2 (33.3)	8 (38.1)	40 (41.2)
Objective response rate	0	1 (12.5)	0	2 (9.5)	6 (6.2)
95% confidence interval [a]	NA	(0.3, 52.7)	NA	(1.2, 30.4)	(2.3, 13.0)
Disease stabilization rate	0	3 (37.5)	1 (16.7)	9 (42.9)	34 (35.1)
95% confidence interval [a]	NA	8.5, 75.5	0.4, 64.1	21.8, 66.0	25.6, 45.4

NA=not applicable.

Notes: Cohorts 01, 02, 03, 04, 05, 06, 07, 08, and 20 (maximum tolerated dose expansion) are associated with the 21/7 dosing regimen. Cohorts 01A, 02A, 03A, 04A, and 30 (maximum tolerated dose expansion) are associated with the 14/14 dosing regimen.

Best overall response was assessed by the investigator per Response Evaluation Criteria in Solid Tumors criteria. Objective response rate was defined as the proportion of patients achieving overall response of confirmed response, partial response, or stable disease. The safety population included all patients who received at least 1 dose of study drug.

a. Exact confidence intervals were obtained using the Clopper-Pearson method.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant submitted a pivotal randomised, double-blind, placebo-controlled Phase III trial GO28141, "coBRIM", comparing vemurafenib plus placebo versus vemurafenib plus cobimetinib in previously untreated BRAF V600-mutation positive patients with unresectable locally advanced or metastatic melanoma. The single-arm, open-label Phase 1b trial NO25395, "BRIM7" and the Phase 1a trial MEK4592g, are considered supportive.

In general, the pivotal study was well conducted, the treatment arms were well balanced and there were no major protocol deviations that affected the robustness of the data. A routine GCP inspection found critical findings with regard to the cleaning of data affecting ORR data in one of the inspected sites. The inspection report concluded that the deviations are generally not considered to be of concern

in the context of the marketing authorisation application. Even the deviations concerning the efficacy parameters seem to have not affected the primary efficacy parameter Progression Free Survival.

The pivotal study compared two treatment arms, a vemurafenib plus cobimetinib arm versus vemurafenib plus placebo and therefore did not contain a third arm of cobimetinib plus placebo. The CHMP expressed some concern over the lack of a cobimetinib only treatment arm. It was considered that the clinical efficacy of cobimetinib monotherapy had not been thoroughly investigated in melanoma patients as only 45 patients with different types of cancer were treated with the same dose/schedule as intended for melanoma patients. The lack of information on the efficacy of cobimetinib monotherapy results in a situation where the efficacy contribution of each of the components in the combination therapy cannot be formally assessed and as a result it is not known whether the added toxicity of vemurafenib could have been avoided. However, there is support from non-clinical data for a stronger effect of combination therapy in BRAF sensitive xenograft tumours. In addition, cross-study comparison of published phase 3 monotherapy data of the BRAF inhibitors vemurafenib[5] and dabrafenib[10] and MEK inhibitor trametinib[9] provided clinical support for a superior efficacy of the combination therapy over the MEK or BRAF inhibitor monotherapy. Therefore, the lack of a cobimetinib only treatment arm was considered acceptable.

The dose schedule for the pivotal study is considered justified based on the data from the single arm study MEK4592g study and NO25395 study. In study NO25395 the evaluation of a 14/14 schedule showed tumour regrowth in some patients during off-drug period whereas a 21/7 schedule showed no tumour regrowth during the off-drug period. Therefore, the current posology is considered acceptable.

Efficacy data and additional analyses

Phase III study GO28141 - coBRIM

Primary efficacy endpoint – *Investigator-assessed Progression-free survival (PFS)*

In the planned primary analysis, the investigator-based PFS (with stratifications) hazard ratio (HR) was 0.51 (95%CI 0.39, 0.68; log-rank p<0.0001) in favour of the cobimetinib plus vemurafenib arm, thus reaching and surpassing the HR of 0.55 aimed for in the design of the study.

In the updated PFS analysis, performed at an event rate of 65% and with data cut-off 8 months after the primary analysis, the HR was 0.58 (95%CI: 0:46; 0.72), the difference in medians across arms was 5.0 months (12.25 vs. 7.2 months).

The pre-planned unstratified PFS analysis (HR = 0.51, 95%CI: 0.39, 0.68; log-rank p<0.0001) was consistent with the stratified analysis, indicating robustness of the data.

Secondary efficacy endpoints

IRF-assessed PFS (not updated)

The HR for IRF-assessed PFS (with stratifications) was 0.60 (95%CI 0.45, 0.79; log-rank; p=0.0003; stratified analysis) in favour of the cobimetinib plus vemurafenib arm. The PFS improvement when assessed by the IRF was consistent with investigator assessment.

The median PFS was 11.3 months (95%CI: 8.5 months, not evaluable) in the cobimetinib plus vemurafenib arm compared with 6.0 months (95% CI: 5.6, 7.5 months) in the placebo plus vemurafenib arm. The unstratified analysis of IRF-assessed PFS was consistent with the stratified analysis (HR =0.61; 95% CI: 0.46, 0.81; p=0.0006).

Overall survival (OS)

Due to the low overall event rate of 85/495 = 17%, an updated OS analysis was requested, which was performed at an event rate of 188/495 = 38%. This is still considered immature. In the planned interim analysis of OS HR=0.645 (stratified) and 0.62 (unstratified), in favour of the cobimetinib plus vemurafenib arm.

In the updated analysis, the OS analysis was consistent: 0.650 (stratified) with a median OS of 17 months in the vemurafenib plus placebo arm, but had not yet been reached for the combination arm. It was noted that the estimate for the lower 95% interval was 5 months apart in the two treatment arms. Thus, these preliminary results from OS analysis are considered supportive of the primary efficacy analysis, investigator–assessed PFS.

Objective response rate (ORR)

In the planned primary analysis based on investigator assessments, the difference in confirmed ORR was 67.6% versus 44.8% for patients treated with cobimetinib plus vemurafenib vs. patients treated with vemurafenib and placebo ($p < 0.0001$ by chi-square with Schouten correction). In the IRF analysis of ORR, a total of 56.3% of patients in the cobimetinib plus vemurafenib arm attained an objective response compared to 40.7% of patients in the vemurafenib plus placebo arm.

The updated analysis showed a confirmed ORR of 69.6% (95% CI: 63.5%, 75.3%) versus 50.0% (95% CI: 43.6%, 56.4%), respectively. Complete response was observed in 16% of patients in the cobimetinib plus vemurafenib arm and 11% of patients in the placebo plus vemurafenib arm.

Duration of Response (DoR)

The median duration of confirmed response, as assessed by investigators, was 7.3 months (95% CI: 5.8 months, not estimable) in the 111 responders in the placebo plus vemurafenib arm and not reached at the time of the clinical cut-off in May 2014 in the 167 patient responders in the cobimetinib plus vemurafenib arm (95% CI: 9.3 months, not estimable). In the IRF analysis, the median duration of confirmed response for the 101 responders in the control arm was 8.2 months (95% CI: 7.5, not estimable) and not reached for the 139 responders in the cobimetinib-containing arm (95% CI: 9.5, not estimable). The proportions with event following response were similar, 17% vs 18%, respectively.

Time to response (TTR)

Swimlane plots gives the impression of similar time-to-response patterns, with a majority of responses reported at two months (i.e. at first tumour assessment) although numerically more responses in the experimental arm. No numerals were presented.

Patient-reported outcomes (PROs)

Global health status/health-related quality of life (HRQoL), symptom severity, and functional interference of symptoms by patient report were measured for each treatment arm using the EORTC QLQ-C30 questionnaire. Completion rates were consistently high among all cycles for both treatment arms (≥ 88%). Patients in the cobimetinib plus vemurafenib arm experienced either clinically meaningful improvement or marginal improvement in insomnia in time points in 4 treatment cycles, and clinically meaningful worsening of diarrhoea from baseline at Day 15 in the two first treatment cycles. For global health status, as well as most functioning and symptom scales, the difference in proportion of responders was small, indicating similarity in HRQoL between the two treatment arms. Larger differences were seen for insomnia and social functioning, and to a lesser extent, pain and fatigue; all favoured the cobimetinib plus vemurafenib arm.

Summary of primary vs. updated analyses

The primary analysis of PFS and ORR showed statistically significant differences between arms (p< 0.0001 for both). The results in the updated analyses were consistent with the primary analyses, with similar or narrower confidence intervals: PFS HR 0.51 and 0.58, OS HR 0.65 and 0.65, (95% CI: 0.49-0.87 for the updated analysis), and difference in ORR 23% and 20%, in the earlier and updated analyses, respectively. It is noted that the CIs for ORR in the two study arms are not overlapping.

Subgroup analyses

Subgroup analyses were consistent with the overall results, with nearly all HR point estimates below 1.0 and near the overall HR of 0.51. For the two subgroups with very few subjects, Non-white or unknown race (n=33) and Prior treatment of brain metastasis (n=3), the HR point estimates were >1.0 with wide confidence intervals. Thus, efficacy in these subgroups is considered unknown.

Some differences between subgroups were noted and the relative efficacy appears generally higher in some subgroups of poorer prognosis (e.g. disease stage M1c, and performance status ECOG 1) compared with their better prognosis counterparts. One of the main causes of mortality in melanoma patients is the development of brain metastases. In the phase 3 study, only 3 patients with brain metastases were treated (2 in combination group, 1 in control group). Therefore, efficacy of combination therapy in treatment of brain metastases is not established. Therefore, the safety and long-term efficacy in patients with brain (CNS) involvement has been included in the RMP as missing information. In addition, a warning has been included in section 4.4 of the SmPC that "The safety and efficacy of the combination of cobimetinib and vemurafenib have not been evaluated in patients with a BRAF V600 mutation-positive melanoma which has metastasised to the brain. The intracranial activity of cobimetinib is currently unknown ", and in section 5.1 where there are no data on the safety or efficacy of cobimetinib in combination with vemurafenib in patients with central nervous system metastasis or in patients with non-cutaneous malignant melanoma. The CHMP has requested the applicant to submit the results of a post-authorisation study to evaluate the safety and efficacy of cobimetinib in combination with vemurafenib in patients with CNS involvement (RMP). Therefore, the applicant is requested to submit the results of the Study ML29155: Phase 2 Study of Cobimetinib in Combination with Vemurafenib in Active Melanoma Brain Metastases (coBRIM-B). Deadline: 31 December 2019.

Phase 1b study, NO25395 - BRIM7

In the dose-escalation combination study NO25395/BRIM7, the highest tested dose regimen was the single-agent maximum tolerated dose (MTD) for both agents, i.e. cobimetinib 60 mg QD Days 1-21 and vemurafenib 960 mg BID Days 1-28 in a 28-day cycle. This was considered tolerable and selected as the recommended Phase II/III dose.

In patients that had not been previously treated with vemurafenib (BRAFi-naïve patients) (all doses, n=63), the confirmed objective response rate was 87%, including a complete response in 10% of patients. The median duration of response was 12.5 months. The median PFS for BRAFi naïve patients was 13.7 months, with median follow-up time of 12.7 months, which is considered clinically significant. In the subgroup of patients who received 60 mg cobimetinib once daily for 21 days (n=39) the efficacy results were similar to the overall BRAFi naïve patients with an objective response rate of 85%. The median duration of response in this group was 11.3 months and the median PFS was 12.7 months.

In patients that progressed after vemurafenib treatment (BRAFi-PD patients), the objective response rate (all doses) was low at 15% (95% CI: 7.5, 25.5); although the median duration of response was of a relevant magnitude in those who had responses, 6.7 months. Median PFS in vemurafenib-PD patients

was 2.8 months (95% CI: 2.63, 3.45). In the subgroup of patients who received 60 mg cobimetinib once daily for 21 days (n=27), the objective response rate was 26 %, while median duration of response was not estimable, and median PFS was 2.8 months.

Genetic differences in PD response

BRAF mutation V600E and V600K

In the phase III study GO28141/coBRIM a lower HR estimate (trend of better relative efficacy) for the vemurafenib (BRAF inhibitor) + cobimetinib (MEK inhibitor) combination arm vs. the vemurafenib + placebo arm was seen in the subgroup with BRAFV600K mutation (HR 0.27, n= 56) compared with the complementary subgroup with BRAFV600E mutation (HR 0.57, n=344). In the updated analysis the difference in PFS HR between patients with V600E and V600K had decreased substantially, however, (HRs 0.64 and 0.52, respectively).

Trends of better relative efficacy for the V600K compared with the V600E subtype have also been seen in the two trametinib registration studies comparing monotherapy dabrafenib (BRAF inhibitor) with combination therapy with dabrafenib and trametinib (MEK inhibitor). In both the phase II study BRF113122 part C (n=108), and in the phase III study MEK115306 (n=423), lower HR point estimates (trends of better relative efficacy) for the combination therapy was seen for V600K mutation.

In the Phase III vemurafenib monotherapy trial NO25026, which compared vemurafenib 960 mg orally twice daily with dacarbazine in patients with previously untreated unresectable Stage IIIC or IV melanoma, the response rate in patients with V600Emutation was 59% and the median PFS 6.9 months, compared with 45% and 5.9 months in patients with V600K mutation[8].

Published results from both the MD Anderson Cancer Center and Melanoma Institute of Australia retrospective studies suggest that the BRAF V600K tumour genotype may be associated with a more aggressive clinical phenotype including a shorter interval between the time of initial melanoma diagnosis to the diagnosis of stage IV disease. However, in the metastatic setting, these associations were not consistently observed[27, 28].

Other V600 mutation subtypes

With regard to other, rarer, V600 subtypes, some support of activity of vemurafenib/cobimetinib therapy is provided by preclinical data. Thus, data from biochemical assays, *in silico* protein structure modelling, and *in vitro* studies on melanoma cell lines have been presented by the Applicant that support the activity of vemurafenib monotherapy in V600 subtypes such as R, D, G, M as well as other BRAF mutations. *In vitro* data showing a similar sensitivity of BRAF V600E and V600D mutated melanoma cell lines to single-agent cobimetinib is also available (not shown).

Clinical support for activity of BRAFi with single-agent vemurafenib in patients with non-E, non-K V600 mutated tumours comes from an ongoing single-arm phase II study ML27763 investigating efficacy in non-E activating mutations, showing similar ORR and median PFS for non-E/non-K (n=17) as for V600K (n=12) mutations at interim analysis. A number of published case reports/series also describe responses to vemurafenib in BRAF mutations of other types thanV600E and V600K (not shown). In addition, the phase 1b study NO25395/BRIM7 included one patient with V600M mutation who responded with PR to the vemurafenib + cobimetinib combination treatment.

BRAF mutation test

The cobas 4800 BRAF V600 Mutation Test (Roche Molecular Systems, Pleasanton, CA, USA) used in the present trials is a clinically validated qualitative test to determine the presence or absence of a BRAF

V600 mutation in melanoma tumour tissue. The cobas test was clinically validated in Study NO25026 the registrational study for Zelboraf (vemurafenib). Although specifically designed to detect the BRAF V600E mutation, the test also cross-reacts with BRAF V600K and other BRAF V600 mutations to yield a mutation-positive call (cobas 4800 BRAF V600 Mutation Test CE package insert). The ability of the cobas test to detect non-E BRAF V600 mutations has been described by Anderson et al.[29] and McArthur et al.[8]. Sanger sequencing of tumour samples from vemurafenib clinical trials confirmed the inclusion of patients whose tumours carried V600K and V600D mutations.

In response to questions the applicant has shown that all V600 mutant alleles detected above the sensitivity cut-off of 5% appeared to be clinically relevant, since when applying different cut-offs, patients with low and high BRAF variant frequencies within each treatment arm had similar PFS. In addition, for all tested cut-offs combination therapy with cobimetinib + vemurafenib was consistently associated with higher PFS than vemurafenib + placebo.

General comments

The CHMP highlighted that in patients that have progressed on BRAF inhibitor therapy, there was the possibility of a loss of chance of patients receiving potentially other treatment options that could provide a better efficacy for this line of therapy. There was the concern that awaiting progression on BRAFi + MEKi after failure on BRAFi, even if only for a few months, could therefore be detrimental to the possibility of response on subsequent therapies such as immunotherapy. The available evidence from the literature suggests that patients that have progressed on BRAF inhibitor have a reactivated MAPK pathway and that their tumours may still respond to downstream targeting of MEK. As a consequence, patients may still derive benefit from further downstream targeting with a MEK inhibitor. There were no clinical or biological markers that could be identified based on the limited data available from biological samples to identify patients with high likelihood of response. Therefore, the CHMP did not restrict the indication to a BRAF inhibitor-naive patient population. The indication includes patients that have progressed on BRAF inhibitor treatment, with a reference to a warning in section 4.4 that patients that have progressed on BRAF inhibitor will derive lower efficacy and that other treatment options could be considered for this patient population.

2.5.4. Conclusions on the clinical efficacy

The overall efficacy results in the pivotal Phase III study GO28141/coBRIM were consistent across all outcome parameters and subgroups analysed. The PFS results were statistically significant and clinically relevant. The results of the Phase III study GO28141/coBRIM showed a clinically relevant efficacy for the combination treatment of cobimetinib and vemurafenib in terms of PFS and ORR in BRAF naive patients and in patients that progressed with BRAF inhibitor therapy. The OS results support the clinical benefit observed in melanoma patients although the magnitude of the treatment effect is yet unknown as the data is still considered immature. As a follow up, the CHMP would recommend to the applicant to submit the results of the final OS analysis of study GO28141. The supportive study NO25395 also showed a clinically relevant efficacy in BRAFi-naive patients as well as for patients whom had previously progressed on vemurafenib (BRAFi-PD), acknowledging that data in this patient population is limited and that the clinical benefit observed in the study indicated that it was lower in these patients. Therefore, other treatment options should be considered before treatment with the combination in this prior BRAF inhibitor treated population. The sequencing of treatments following progression on a BRAF inhibitor therapy has not been established. A recommendation has been included in the SmPC in section 4.4 for patients that have progressed following BRAF inhibitor therapy.

The safety and efficacy of Cotellic in children and adolescents below 18 years of age have not been established. No data are available (SmPC section 4.2). The treatment in patients < 18 years of age has

been included as missing information and CHMP has requested, as part of the PIP, the submission of the results from two paediatric studies in patients 6 months to 18 years of age (GO29665). The studies will evaluate safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy dose finding study and confirmatory safety and efficacy trial in patients 6 months to < 18 years of age.

The CHMP considers the following measures necessary to address issues related to efficacy:

- The safety and efficacy of cobimetinib in combination with vemurafenib in patients with CNS involvement is unknown. Therefore, the applicant is requested to submit the results of the Study ML29155: Phase 2 Study of Cobimetinib in Combination with Vemurafenib in Active Melanoma Brain Metastases (coBRIM-B). Deadline: 31 December 2019.

2.6. Clinical safety

Patient exposure

The clinical safety has been addressed in the studies reported in Table 53.

Table 53: Patient exposure to cobimetinib (as single agent or in combination with vemurafenib)

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with ≥ 6 months safety data
GO28141 (Phase III, double blind, randomized)	495	247	BRAFi naïve: 247	N/A
NO25395 (Phase Ib, open- label, dose-escalation and expansion, combination)	131	129 – cobimetinib + vemurafenib BRAFi naïve: 63 vemurafenib-PD: 66 2 – cobimetinib monotherapy	BRAFi naïve: 39 Vemurafenib-PD: 27	N/A
MEK4592g (Phase 1, single- agent, open-label, dose-escalation study, monotherapy)	119	115	45	N/A

Phase 3 Randomised Study GO28141

The exposure of cobimetinib and vemurafenib is reported in Table 54 and Table 55, respectively.

Table 54: Extent of Exposure of Cobimetinib or Placebo (Safety Population)

	GO28141 placebo + vemurafenib n=246	GO28141 cobimetinib + vemurafenib n=247	NO25395 cobimetinib + vemurafenib n=129	Integrated Safety Population n=376
Duration of Treatment Period (Days)				
Mean (SD)	205.8 (130.1)	243.4 (140.2)	312.9 (269.3)	267.3 (196.8)
Median	172.5	267	211	251.5
Min, Max	5 - 515	4 - 563	14 - 998	4 – 998
Number of Cycles Received				
Mean (SD)	7.7 (4.7)	9.1 (5.0)	11.5 (9.5)	9.9 (7.0)
Median	6.0	10.0	8.0	9.0
Min, Max	1 - 18	1 - 21	1 - 32	1 – 32
Average Dose Taken Per Day (mg/day)				
Mean (SD)	43.56 (7.17)	41.43 (9.30)	43.75 (7.78)	42.23 (8.86)
Median	45.21	44.06	44.89	44.47
Min, Max	18.2 - 64.0	11.6 - 60.0	17.3 - 68.3	11.6 - 68.3
Percent Dose Intensity				
Mean (SD)	92.62 (13.70)	87.12 (16.74)	92.78 (13.80)	89.07 (16.01)
Median	99	96.6	98.76	97.61
Min, Max	39.7 - 110.5	25.0 - 108.2	34.5 - 109.6	25.0 - 109.6

SD = standard deviation; Min = minimum; Max = maximum.
The safety update data cut-off dates for each study are: GO28141, 19 September 2014; NO25395, 5 September 2014.

Table 55: Extent of Exposure of Vemurafenib (Safety Population)

	GO28141 placebo + vemurafenib n=246	GO28141 cobimetinib + vemurafenib n=247	NO25395 cobimetinib + vemurafenib n=129	Integrated Safety Population n=376
Duration of Treatment Period (Days)				
Mean (SD)	210.3 (127.6)	253.1 (138.3)	312.0 (267.9)	273.3 (194.5)
Median	175.0	279	201	266.5
Min, Max	5 - 516	9 - 563	14 - 998	9 – 998
Number of Cycles Received				
Mean (SD)	7.7 (4.6)	9.3 (5.0)	11.3 (9.4)	10.0 (6.9)
Median	7.0	10.0	8.0	9.5
Min, Max	1 - 18	1 - 21	1 - 32	1 – 32
Average Dose Taken Per Day (mg/day)				
Mean (SD)	1638.23 (349.98)	1642.74 (329.37)	1570.85 (298.80)	1618.07 (320.64)
Median	1856.33	1813.33	1463.41	1750.99
Min, Max	746.6 – 2194.4	445.6 - 1981.1	727.9 - 1920.0	445.6 - 1981.1
Percent Dose Intensity				
Mean (SD)	85.32 (18.23)	85.56 (17.16)	91.05 (13.52)	87.44 (16.19)
Median	96.69	94.44	97.3	95.7
Min, Max	38.9 – 114.3	23.2 - 103.2	47.9 - 123.3	23.2 - 123.3

SD = standard deviation; Min = minimum; Max = maximum.
The safety update data cut-off dates for each study are: GO28141, 19 September 2014; NO25395, 5 September 2014.

Adverse events

The common AEs regardless of relationship to study drug at the original cut-off (09 May 2014) and at the updated cut-off (19 September 2014) are shown in Table 56.

Table 56: Common Adverse Events Regardless of Relationship to Study Drug That Occurred in 10% or More of Patients in Either Arm in the Pivotal Study GO28141 (Safety Population)

	Placebo + Vemurafenib		Cobimetinib + Vemurafenib	
	SCS n=239	safety update n=246	SCS n=254	safety update n=247
Patient experiencing event, n (%)				
Total number of patients with at least one AE	233 (97.5)	240 (97.6)	250 (98.4)	244 (98.8)
Diarrhea	67 (28.0)	76 (30.9)	144 (56.7)*	148 (59.9)*
Nausea	57 (23.8)	62 (25.2)	99 (39.0)*	102 (41.3)*
Rash	85 (35.6)	94 (38.2)	99 (39.0)*	98 (39.7)
Arthralgia	96 (40.2)*	99 (40.2)*	83 (32.7)	89 (36.0)
Fatigue	74 (31.0)	80 (32.5)	82 (32.3)	85 (34.4)
Photosensitivity reaction	38 (15.9)	45 (18.3)	72 (28.3)*	82 (33.2)*
Increased blood CPK	7 (2.9)	7 (2.8)	76 (29.9)*	80 (32.4)*
Pyrexia	53 (22.2)	56 (22.8)	66 (26.0)*	69 (27.9)*
Increased ALT	43 (18.0)	44 (17.9)	60 (23.6)*	61 (24.7)*
Vomiting	29 (12.1)	31 (12.6)	54 (21.3)*	60 (24.3)*
Increased AST	30 (12.6)	31 (12.6)	56 (22.0)*	58 (23.5)*
Pruritus	41 (17.2)	46 (18.7)	47 (18.5)	48 (19.4)
Increased GGT	41 (17.2)	43 (17.5)	44 (17.3)	47 (19.0)
Decreased appetite	46 (19.2)	50 (20.3)	48 (18.9)	46 (18.6)
Asthenia	33 (13.8)	40 (16.3)	44 (17.3)*	43 (17.4)
Headache	36 (15.1)	39 (15.9)	36 (14.2)	41 (16.6)
Alopecia	70 (29.3)*	73 (29.7)*	35 (13.8)	37 (15.0)
Dysgeusia	25 (10.5)	26 (10.6)	33 (13.0)*	37 (15.0)*
Hypertension	19 (7.9)	19 (7.7)	36 (14.2)*	37 (15.0)*
Increased blood ALP	19 (7.9)	22 (8.9)	35 (13.8)*	36 (14.6)*
Rash maculo-papular	37 (15.5)	38 (15.4)	37 (14.6)	38 (15.4)

	Placebo + Vemurafenib		Cobimetinib + Vemurafenib	
	SCS n=239	safety update n=246	SCS n=254	safety update n=247
Patient experiencing event, n (%)				
Dry Skin	37 (15.5)*	39 (15.9)	31 (12.2)	35 (14.2)
Sunburn	38 (15.9)*	43 (17.5)*	33 (13.0)	34 (13.8)
Dermatitis acneiform	22 (9.2)	22 (8.9)	33 (13.0)*	34 (13.8)*
Blood creatinine increased	18 (7.5)	20 (8.1)	29 (11.4)*	34 (13.8)*
Anemia	17 (7.1)	20 (8.1)	26 (10.2)*	32 (13.0)*
Edema peripheral	25 (10.5)	28 (11.4)	27 (10.6)	31 (12.6)
Chorioretinopathy	1 (0.4)	1 (0.4)	30 (11.8)*	31 (12.6)*
Myalgia	23 (9.6)	30 (12.2)	26 (10.2)	28 (11.3)
Hyperkeratosis	68 (28.5)*	75 (30.5)*	26 (10.2)	27 (10.9)
Vision blurred	5 (2.1)	6 (2.4)	23 (9.1)*	25 (10.1)*
Erythema	30 (12.6)*	33 (13.4)*	21 (8.3)	24 (9.7)
Pain in extremity	32 (13.4)*	35 (14.2)*	19 (7.5)	24 (9.7)
Constipation [a]	25 (10.5)	26 (10.6)	23 (9.1)	24 (9.7)
Cough	26 (10.9)*	30 (12.2)*	18 (7.1)	19 (7.7)
Abdominal pain	18 (7.5)	19 (7.7)	24 (9.4)	25 (10.1)*
Skin papilloma	25 (10.5)*	29 (11.8)*	11 (4.3)	12 (4.9)
SCC of skin	27 (11.3)*	31 (12.6)*	7 (2.8)	8 (3.2)
Keratosis pilaris	22 (9.2)	26 (10.6)*	8 (3.1)	8 (3.2)

AE = adverse events; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gammaglutamyltransferase; SCC = squamous cell carcinoma; SCS = Summary of Clinical Safety (cut-off 09 May 2014).
a The preferred term of constipation should have been, but was not, included.
*Asterisks indicate the population in which the AE occurred at a higher frequency (>2% difference in frequency between respective populations at each cut-off date).
Safety update data cut-off date: 19 September 2014.

The causal relationship of a reported adverse event to cobimetinib was based on the comparative incidence of adverse events in patients treated with cobimetinib in combination with vemurafenib (active arm) and vemurafenib plus placebo (control arm). The criteria by which cobimetinib ADRs were defined are adverse events (all grades) that occurred with a ≥ 5% incidence over the control arm or Grades 3-4 adverse events with an incidence of ≥ 2% over the control arm were assessed as

causally related with cobimetinib. Thus, these are considered ADRs for the product. Adverse events that did not meet the ADR criteria of a ≥ 5% incidence over the control arm for all Grades or Grades 3-4 adverse events with an incidence of ≥ 2% over the control arm, or occurred at the same or lower frequency in the active arm compared to the control arm (e.g., fatigue, cough, dysgeusia, headache, and arthralgia) were not considered as causally related to cobimetinib. Amongst all adverse events reported in study GO28141, causality was not assessed for both cobimetinib and vemurafenib as a combination together because of the lack of a pure placebo treatment arm, and therefore no ADRs are considered as combination ADRs. The exception to the above criteria were events of cutaneous squamous cell carcinoma (cuSCC), keratoacanthomas and other hyperkeratotic skin lesions, which are well-recognised toxicities associated with BRAF inhibitors, including vemurafenib and, therefore, were considered ADRs with cobimetinib. The list of ADRs for cobimetinib treatment is displayed in Table 57.

Table 57: Adverse Drug Reactions in Patients treated with Cotellic in Combination with Vemurafenib in Study GO28141

ADRs	Phase III study: GO28141				Frequency[a] (All Grades)
	Cotellic + Zelboraf (n = 254)		Placebo + Zelboraf (n = 239)		
	All grades (%)	Grade 3-4 (%)	All grades (%)	Grade 3-4 (%)	
Blood and lymphatic system					
Anaemia	10	1	7	2	very common
Eye Disorders					
Chorioretinopathy[b]	12	<1	<1	-	very common
Vision Blurred	9	-	2	-	common
Retinal Detachment[b]	8	2	-	-	common
Visual Impairment	3	-	-	-	common
Gastrointestinal disorders					
Diarrhea	57	6	28	-	very common
Nausea	39	1	24	1	very common
Vomiting	21	1	12	1	very common
General disorders and administration site conditions					
Pyrexia	26	2	22	-	very common
Chills	8	-	5	-	common

ADRs	Phase III study: GO28141				Frequency[a] (All Grades)
	Cotellic + Zelboraf (n = 254)		Placebo + Zelboraf (n = 239)		
	All grades (%)	Grade 3-4 (%)	All grades (%)	Grade 3-4 (%)	
Investigations					
Blood CPK increased	30	10	3	-	very common
ALT increased	24	11	18	6	very common
AST increased	22	8	13	2	very common
GGT increased	17	12	17	10	very common
Blood ALP increased	14	4	8	2	very common
Decreased Ejection Fraction	8	1	3	1	common
Blood bilirubin increased	8	1	6	1	common
Metabolism and nutrition disorders					
Dehydration	4	2	1	-	common
Hypophosphatemia	4	2	<1	-	common
Hyponatremia	4	2	1	<1	common
Hyperglycaemia	3	1	1	-	common
Neoplasms benign, malignant and unspecified					
Basal Cell Carcinoma	4	4	2	2	common
Cutaneous squamous cell carcinoma	3	2	11	11	common
Keratoacanthoma	1	1	8	8	common
Respiratory, thoracic and mediastinal disorders					
Pneumonitis	1	-	<1	-	Common

ADRs	Phase III study: GO28141				Frequency[a] (All Grades)
	Cotellic + Zelboraf (n = 254)		Placebo + Zelboraf (n = 239)		
	All grades (%)	Grade 3-4 (%)	All grades (%)	Grade 3-4 (%)	
Skin and subcutaneous tissue disorders					
Photosensitivity[c]	41	3	31	-	very common
Rash	39	6	36	5	very common
Rash maculo-papular	15	6	16	5	very common
Dermatitis acneiform	13	2	9	2	very common
Hyperkeratosis	10	-	29	2	very common
Vascular Disorders					
Hypertension	14	4	8	3	very common
Haemorrhage[d]	10	1	6	<1	very common

[a] Based on the Phase III study GO28141 adverse events of all grades

[b] Serous retinopathy, including events of chorioretinopathy and retinal detachment

[c] Combined figure includes reports of photosensitivity reaction, sunburn, solar dermatitis, actinic elastosis

[d] All bleeding events (all types and Grades: 10% vs 6%). Higher frequencies in the Cotellic plus vemurafenib arm were observed for cerebral haemorrhage (1% vs 0%), gastrointestinal tract hemorrhage (3% vs 1%), reproductive system hemorrhage (2% vs 1%) and haematuria (2% vs 1%)

For BRAFi-naïve patients in the phase 1b NO25395 study, the most common AEs were diarrhoea as seen in 82%, nausea in 57%, vomiting in 43%, fatigue in 70%, pyrexia in 43%, arthralgia in 48%.

In the cobimetinib monotherapy study MEK4592g, the most frequent AEs among all subjects were diarrhoea (67.0%), fatigue (50.4%), rash (49.6%), nausea, vomiting (33.9% each), oedema peripheral (28.7%), abdominal pain (24%) and constipation (21%).

A comparison of the Adverse Events by intensity for studies GO28141 and NO25395 are summarized in Table 58.

Table 58: Overview of Adverse Events intensities for studies GO28141 and NO25395

	GO28141				NO25395 Cobimetinib + Vemurafenib						Integrated Safety Population	
	Placebo + Vemurafenib		Cobimetinib + Vemurafenib		BRAFi-naïve Patients n=63		Vemurafenib-PD Patients n = 66		All Patients n=129			
	SCS n=239	safety update n = 246	SCS n=254	safety update n = 247	SCS	safety update	SCS	safety update	SCS	safety update	SCS n=383	safety update n = 376
Total number (%) of patients with ≥ 1 AE	233 (97.5)	240 (97.6)	250 (98.4)	244 (98.8)	63 (100)	63 (100)	64 (97.0)	64 (97.0)	127 (98.4)	127 (98.4)	377 (98.4)	371 (98.7)
Total number of patients (%) with ≥ 1:												
Grade ≥3 AEs	142 (59.4)	146 (59.3)	165 (65.0)	176 (71.3)	49 (77.8)	51 (81.0)	31 (47.0)	32 (48.5)	80 (62.0)	83 (64.3)	245 (64.0)	259 (68.9)
Grade 5 AEs [a]	3 (1.3)	3 (1.2)	6 (2.4)	5 (2.0)	0	1 (1.6)	0	0	0	1 (0.8)	6 (1.6)	6 (1.6)
SAEs	60 (25.1)	64 (26.0)	75 (29.5)	85 (34.4)	25 (39.7)	31 (49.2)	18 (27.3)	18 (27.3)	43 (33.3)	49 (38.0)	118 (30.8)	134 (35.6)
AEs leading to discontinuation of cobimetinib / placebo	33 (13.8)	24 (9.8) [c]	42 (16.5)	47 (19.0)	3 (4.8)	6 (9.5)	1 (1.5)	1 (1.5)	4 (3.1)	7 (5.4)	46 (12.0)	54 (14.4)
AEs leading to discontinuation of vemurafenib	32 (13.4)	24 (9.8) [c]	35 (13.8)	39 (15.8)	4 (6.3)	6 (9.5)	3 (4.5)	3 (4.5)	7 (5.4)	9 (7.0)	42 (11.0)	48 (12.8)
AEs leading to discontinuation of cobimetinib and vemurafenib [b]	28 (11.7)	20 (8.1)	32 (12.6)	37 (15.0)	2 (3.2)	4 (6.3)	1 (1.5)	1 (1.5)	3 (2.3)	5 (3.9)	35 (9.1)	42 (11.2)

SCS = Summary of Clinical Safety (cut-off 09 May 2014), Safety update data cut-off date: 19 September 2014

The most common Grade ≥ 3 AEs reported at a higher frequency (≥ 2% difference) in patients treated with cobimetinib plus vemurafenib than in patients treated with placebo plus vemurafenib are reported in Table 59.

Table 59: Grade ≥ 3 Adverse Events Occurring in at Least 2% of Patients in Either Arm (Safety-Evaluable Population, Study GO28141)

	Placebo + Vemurafenib		Cobimetinib + Vemurafenib	
	SCS n=239	safety update n=246	SCS n=254	safety update n=247
Patient experiencing event, n (%)				
Total number of patients with at least one AE	142 (59.4)	146 (59.3)	165 (65.0)	176 (71.3)
Increased GGT	25 (10.5)	25 (10.2)	30 (11.8)	32 (13.0)*
Increased ALT	15 (6.3)	15 (6.1)	29 (11.4)*	28 (11.3)*
Increased blood CPK	0	0	26 (10.2)*	28 (11.3)*
Increased AST	5 (2.1)	5 (2.0)	21 (8.3)*	21 (8.5)*
Rash maculo-papular	13 (5.4)	13 (5.3)	16 (6.3)	17 (6.9)
Diarrhea	0	2 (0.8)	16 (6.3)*	16 (6.5)*
Rash	12 (5.0)	14 (5.7)	15 (5.9)	13 (5.3)
Hypertension	6 (2.5)	6 (2.4)	10 (3.9)	11 (4.5)*
BCC	5 (2.1)	6 (2.4)	10 (3.9)	11 (4.5)*
Fatigue	8 (3.3)	7 (2.8)	10 (3.9)	10 (4.0)
Increased blood ALP	4 (1.7)	4 (1.6)	11 (4.3)*	10 (4.0)*
SCC of Skin	27 (11.3)*	31 (12.6)*	6 (2.4)	7 (2.8)
Photosensitivity reaction	0	0	6 (2.4)*	7 (2.8)*
Arthralgia	12 (5.0)*	12 (4.9)*	6 (2.4)	6 (2.4)
Dermatitis acneiform	4 (1.7)	3 (1.2)	6 (2.4)	6 (2.4)
Hyponatraemia	1 (0.4)	1 (0.4)	6 (2.4)*	6 (2.4)*
Retinal detachment	0	0	6 (2.4)*	6 (2.4)*
Asthenia	3 (1.3)	3 (1.2)	5 (2.0)	5 (2.0)
Lipase increased	2 (0.8)	2 (0.8)	5 (2.0)	5 (2.0)
Dehydration	0	0	5 (2.0)*	5 (2.0)*
Anemia	4 (1.7)	6 (2.4)	3 (1.2)	4 (1.6)
Keratoacanthoma	18 (7.5)*	20 (8.1)*	2 (0.8)	3 (1.2)
Pain in extremity	6 (2.5)	6 (2.4)	3 (1.2)	3 (1.2)
Myalgia	6 (2.5)*	6 (2.4)*	1 (0.4)	1 (0.4)
Hyperkeratosis	5 (2.1)*	6 (2.4)*	0	0

SCS = Summary of Clinical Safety (cut-off 09 May 2014)
Safety update data cut-off date: 19 September 2014

Adverse Events of Special Interest

An overview of the AEs of special interest is provided in Table 60.

Table 60: Summary of Patients Experiencing Adverse Events of Special Interest in Studies GO28141 and NO25395, and in the Integrated Safety Population

AESIs	GO28141 placebo + vemurafenib		GO28141 cobimetinib + vemurafenib		NO25395 cobimetinib + vemurafenib n = 129		Integrated Safety Population	
	SCS n=239	safety update n=246	SCS n=254	safety update n=247	SCS	safety update	SCS n = 383	safety update n = 376
Patient experiencing event, n (%)								
Ocular events								
RVO, all grades	0	1 (0.4)	0	1 (0.4)	0	0	0	1 (0.3)
Serous retinopathy, all grades	5 (2.1)	7 (2.8)	61 (24.0)	63 (25.5)	8 (6.2)	7 (5.4)	69 (18.0)	70 (18.6)
Grade ≥ 2 visual disturbances (not including RVO or serous retinopathy events)	16 (6.7)	20 (8.1)	19 (7.5)	25 (10.1)	12 (9.3)	12 (9.3)	31 (8.1)	37 (9.8)
Grade ≥ 3 photosensitivity	0	0	8 (3.1)	9 (3.6)	3 (2.3)	3 (2.3)	11 (2.9)	12 (3.2)
Grade ≥ 2 reduction in LVEF	7 (2.9)	9 (3.7)	17 (6.7)	21 (8.5)	1 (0.8)	2 (1.6)	18 (4.7)	23 (6.1)
Grade ≥ 3 elevation in liver laboratory test [a]	36 (15.1)	36 (14.6)	52 (20.5)	53 (21.5)	16 (12.4)	17 (13.2)	68 (17.8)	70 (18.7)
Cutaneous primary malignancy	47 (19.7)	53 (21.5)	21 (8.3)	26 (10.5)	18 (14.0)	20 (15.5)	39 (10.2)	46 (12.2)
Grade ≥ 3 QTc interval prolongation	4 (1.7)	4 (1.6)	4 (1.6)	4 (1.6)	6 (4.7)	6 (4.7)	10 (2.6)	10 (2.7)
Grade ≥ 3 CPK elevations	1 (0.4)	1 (0.4)	26 (10.2)	28 (11.3)	3 (2.3)	3 (2.3)	29 (7.6)	31 (8.2)
Secondary non-cutaneous primary malignancies	10 (4.2)	8 (3.3)	2 (0.8)	5 (2.0)	3 (2.3)	4 (3.1)	5 (1.3)	9 (2.4)
Grade ≥ 3 rash	38 (15.9)	40 (16.3)	41 (16.1)	40 (16.2)	13 (10.1)	13 (10.1)	54 (14.1)	53 (14.1)

SCS = Summary of Clinical Safety (cut-off 09 May 2014)
Safety update data cut-off date: 19 September 2014
RVO = Retinal Vein Occlusion

Ocular events

This broader term has been introduced and include AESIs of retinal vein occlusion (RVO), serous retinopathy, and other Grade ≥ 2 visual disturbances.

One patient in each arm experienced an event that fell in the retinal vein occlusion (RVO) group terms between the clinical cut-off dates: one Grade 3 event of retinal ischemia in the cobimetinib plus vemurafenib arm which resulted in discontinuation of both cobimetinib and vemurafenib, and one Grade 1 event of retinal vascular disorder in the placebo plus vemurafenib arm which did not result in any dose modification or discontinuation of either placebo or vemurafenib.

The frequency of serous retinopathy AEs in Study GO28141 was similar between the two clinical cut-offs, and remained higher in the cobimetinib plus vemurafenib arm than in the placebo plus vemurafenib arm. The majority of these events remained Grade 1 or Grade 2.

Regarding Grade ≥ 2 Visual Disturbances (not including RVO or serous retinopathy events), the preferred terms included 1 event each of visual impairment, uveitis, cataract, iridocyclitis, diplopia, eye

irritation, maculopathy, retinal degeneration, and corneal edema. All of the new events were Grade 2, and were not suggestive of serous retinopathy or RVO.

Grade ≥ 3 Photosensitivity

In Study GO28141, Grade ≥ 3 photosensitivity events were reported only in the cobimetinib plus vemurafenib arm. Review of photosensitivity events included the preferred terms of photosensitivity reaction, solar dermatitis, and sunburn. These events were reported, respectively, in 6 patients (2.4%), 1 patient (0.4%), and 1 patient (0.4%). The overall pattern of Grade ≥ 3 photosensitivity events in the safety update is consistent with data originally reported.

Grade ≥ 2 reduction in LVEF

In Study GO28141, all reported AEs of reduction in LVEF were Grade 2 or Grade 3. The frequency of Grade ≥ 2 reduction in LVEF events was higher in the cobimetinib plus vemurafenib arm (17 [6.7%] patients) than in the placebo plus vemurafenib arm (7 [2.9%] patients).

As a result of these AEs in the cobimetinib plus vemurafenib arm, 2 patients discontinued cobimetinib, 3 patients had dose interruptions of cobimetinib, 4 patients had dose reductions of cobimetinib, and one patient had dose interruption of vemurafenib. The events were considered resolved in 15 of 17 patients at the clinical cutoff.

As a result of the AEs in the placebo plus vemurafenib arm, 2 patients discontinued from placebo, 2 had dose interruptions of placebo, 1 had a dose reduction of placebo, and 1 had a dose interruption of vemurafenib. The events were considered resolved in 3 out of 7 patients at the clinical cutoff date.

Grade ≥ 3 Liver Laboratory Test Abnormalities

Elevations in liver laboratory tests and liver injury have been associated with vemurafenib use (see vemurafenib SmPC). Therefore , Study GO28141 considers Grade ≥ 3 liver laboratory test abnormalities an adverse event of special interest.

Liver laboratory test abnormalities (Grade ≥ 3) were reported more frequently in patients who received cobimetinib plus vemurafenib than in patients who received placebo plus vemurafenib (20.5% vs. 15.1%). The Grade ≥ 3 liver laboratory test abnormalities that occurred at a ≥ 2% frequency in the cobimetinib plus vemurafenib arm were ALT increased (11.4% vs 6.3%), AST increased (8.3% vs 2.1%), and alkaline phosphatase increased (4.3% vs 1.7%). There was a <2% difference between the two arms for the events of GGT increased, bilirubin increased, liver function test abnormal, and transaminase increased. A patient who received cobimetinib plus vemurafenib was reported to have an AE of drug induced liver injury.

The overall pattern of elevations in liver laboratory tests in the safety update is consistent with data originally reported.

Grade ≥ 3 QTc Interval Prolongation

In Study GO28141, the incidence of potential Grade ≥ 3 QTc prolongation group term events was comparable between the two arms, with events occurring in 1.6% of patients in the cobimetinib plus vemurafenib arm and 1.7% in the placebo plus vemurafenib arm. One patient from each study arm discontinued both study drugs because of Grade ≥ 3 QTc prolongation. Additionally, two events of syncope and one report of cardiac arrest were reported in the cobimetinib plus vemurafenib arm, and 1 report of syncope was reported in the placebo plus vemurafenib arm. None of the patients with reports of syncope or Grade 5 cardiac arrest had concurrent AEs of QTc prolongation reported. 0.4% of

patients in the cobimetinib plus vemurafenib arm and 1.3% in the placebo plus vemurafenib arm had events reported with the specific preferred term “electrocardiogram QT prolonged”.

Any Cutaneous Malignancy

At the original cut-off date (09 May 2014), all cutaneous primary malignancy events in Study GO28141 were reported as Grade 3, as directed in the study protocol. The incidence of any cutaneous primary malignancy was lower in the cobimetinib plus vemurafenib arm (8.3%) than in the placebo plus vemurafenib arm (19.7%). The most common cutaneous malignancies observed were squamous cell carcinoma of skin and keratoacanthoma, reported at lower frequencies among patients treated with cobimetinib plus vemurafenib (2.8% and 0.8%, respectively) than among patients treated with placebo plus vemurafenib (11.3% and 8.4%, respectively). No patients in either treatment arm discontinued the study or cobimetinib or vemurafenib treatment due to a cutaneous malignancy adverse event. As of the clinical cut-off date for the safety update, time to first incidence of cuSCC or KA events continued to be delayed in the cobimetinib plus vemurafenib arm compared with the placebo plus vemurafenib arm, with medians of 4.3 months vs. 1.9 months, respectively, compared with 3.3 vs. 1.8 months. In Study GO28141, the frequency of basal cell carcinoma BCC remained higher in patients in the cobimetinib plus vemurafenib arm than in the placebo plus vemurafenib arm (4.5% vs. 2.4%).

Grade ≥ 3 Rash

The frequency of rash in Study GO28141 was similar in both treatment arms, with Grade ≥ 3 rash reported in 16.1% of patients in the cobimetinib plus vemurafenib arm and in 15.9% of the placebo plus vemurafenib arm (cut-off 09 May 2014). The incidences of individual preferred terms, including (most commonly) maculo-papular rash and rash, were also similar between the two treatment arms.

Diarrhea

At the safety update cut-off date, diarrhoea (preferred term) remained as the most commonly reported AE in the cobimetinib plus vemurafenib arm: sixteen patients (6.5%) in the cobimetinib plus vemurafenib arm experienced Grade 3 diarrhoea vs. 2 patients (0.8%) in the placebo plus vemurafenib arm. The number of SAEs of diarrhoea remained unchanged between the cut-off dates.

The events of diarrhoea (all grades) occurred earlier during treatment in the cobimetinib plus vemurafenib arm when compared to the placebo plus vemurafenib arm. The median time to first event of diarrhoea was 0.4 month in the cobimetinib plus vemurafenib arm and 2.0 months in the placebo plus vemurafenib arm.

Haemorrhage

The incidence of hemorrhagic events was higher in the cobimetinib plus vemurafenib arm (13.0%) than in the placebo plus vemurafenib arm (7.3%) in study GO28141. In both treatment arms, the majority of the hemorrhagic events were Grade 1 or 2 and non-serious.

Pneumonitis/interstitial lung disease

In all, there were 5 cases of pneumonitis/interstitial lung disease reported in study GO28141. A causal relation to cobimetinib and vemurafenib was suspected in 2 serious cases. No new pneumonitis events occurred in either arm in Study GO28141 or in Study NO25395.

Hypertension

At the safety update cut-off date, events of hypertension were reported in 39 patients (15.8%) in the cobimetinib plus vemurafenib arm and in 20 patients (8.1%) in the placebo plus vemurafenib arm in study GO28141. One new SAE of hypertensive crisis (baseline blood pressure 126/77 mmHg) was

reported in the cobimetinib plus vemurafenib arm, which resolved with treatment (medications), and the study drug doses were not changed. The majority of hypertension events were Grade 1 or 2, with a higher proportion of these occurring in the cobimetinib plus vemurafenib arm (10.5% vs. 5.7%), and there were no Grade 4 or 5 events in either group. Upon analysis, there was no apparent correlation between cases of hypertension and those of LVEF reduction.

Hyperglycemia

At the safety update, 11 patients (4.5%) in the cobimetinib plus vemurafenib arm and 3 patients (1.2%) in the placebo plus vemurafenib arm of study GO28141 reported events of hyperglycemia. The majority of events in the cobimetinib plus vemurafenib arm were non-serious and Grade 1 or 2 and no new Grade ≥ 3 events were reported between the two clinical cut-off dates.

Serious adverse event / deaths / other significant events

Serious Adverse Events

SAEs occurred in the Study GO28141 are shown in Table 61.

Table 61: Serious Adverse Events Occurring in At Least 1% of Patients in the Pivotal Study GO28141 (Safety Population)

	Placebo + Vemurafenib		Cobimetinib + Vemurafenib	
	SCS n=239	safety update n=246	SCS n=254	safety update n=247
Patient experiencing event, n (%)				
Total number of patients with at least one SAE	60 (25.1)	64 (26.0)	75 (29.5)	85 (34.4)
Pyrexia	3 (1.3)	3 (1.2)	6 (2.4)*	7 (2.8)*
Dehydration	0	0	5 (2.0)*	5 (2.0)*
Rash	1 (0.4)	1 (0.4)	4 (1.6)*	4 (1.6)*
Retinal detachment	0	0	3 (1.2)*	4 (1.6)*
Pneumonia	2 (0.8)	3 (1.2)	2 (0.8)	4 (1.6)
Rash maculo-papular	2 (0.8)	2 (0.8)	3 (1.2)	3 (1.2)
Increased ALT	1 (0.4)	2 (0.8)	3 (1.2)	3 (1.2)
Increased AST	1 (0.4)	2 (0.8)	3 (1.2)	3 (1.2)
Atrial fibrillation	0	1 (0.4)	3 (1.2)*	3 (1.2)*
Chorioretinopathy	0	0	3 (1.2)*	3 (1.2)*
Diarrhea	0	0	3 (1.2)*	3 (1.2)*
Hypersensitivity	0	0	3 (1.2)*	3 (1.2)*
Convulsion	0	0	1 (0.4)	3 (1.2)
Keratoacanthoma	3 (1.3)*	3 (1.2)*	0	0
Pleural effusion	3 (1.3)*	3 (1.2)	0	0
Pericardial effusion	1 (0.4)	3 (1.2)	1 (0.4) [a]	0 [a]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SAE = serious adverse events; SCS = Summary of Clinical Safety.

Shaded columns indicated the data included in the Summary of Clinical Safety in the NDA.

* Asterisks indicate the population in which the SAE occurred at a higher frequency (>1% difference in frequency between arms).

[a] Patient 2273 who experienced an SAE of pericardial effusion was reported in the cobimetinib plus vemurafenib arm in the NDA. But at the safety update, it was confirmed that this patient only received doses of placebo plus vemurafenib, and therefore, was reassigned back to the placebo plus vemurafenib arm for the safety update analysis. Therefore, the rate of SAE of pericardial effusion in the cobimetinib plus vemurafenib arm decreased from 0.4% to 0% between the two clinical cut-off dates.

Source: GO28141/t_ae_gradesub_ser.

Safety update data cut-off: 19 September 2014.

Deaths

An overview of deaths and Grade 5 AEs are reported in Table 62 and Table 63, respectively.

Table 62: Deaths and Cause of Deaths in Studies GO28141 and NO25395, and the Integrated Safety Population (Safety Population)

	GO28141				NO25395 Cobimetinib + Vemurafenib						Integrated Safety Population	
	Placebo + Vemurafenib		Cobimetinib + Vemurafenib		BRAFi-naïve Patients n=63		Vemurafenib-PD Patients n=66		All Patients n=129			
	SCS n=239	safety update n=246	SCS n=254	safety update n=247	SCS	safety update	SCS	safety update	SCS	safety update	SCS n=383	safety update n = 376
Patient who died, n (%)												
All Deaths	48 (20.1)	82 (33.3)	36 (14.2)	62 (25.1)	12 (19.0)	25 (39.7)	45 (68.2)	52 (78.8)	57 (44.2)	77 (59.7)	93 (24.3)	139 (37.0)
<= 30 days from last dose of treatment	20 (8.4)	26 (10.6)	13 (5.1)	13 (5.3)	4 (6.3)	8 (12.7)	15 (22.7)	15 (22.7)	19 (14.7)	23 (17.8)	32 (8.4)	36 (9.6)
> 30 days from last dose of treatment	28 (11.7)	53 (21.5)	23 (9.1)	47 (19.0)	8 (12.7)	17 (27.0)	30 (45.5)	37 (56.1)	38 (29.5)	54 (41.9)	61 (15.9)	101 (26.9)
Primary Cause of Death												
Disease Progression	46 (19.2)	76 (30.9)	31 (12.2)	54 (21.9)	12 (19.0)	24 (38.1)	43 (65.2)	50 (75.8)	55 (42.6)	74 (57.4)	86 (22.5)	128 (34.0)
Adverse Event	1 (0.4)	2 (0.8)[a]	2 (0.8)	5 (2.0)	0	1 (1.6)	0	0	0	1 (0.8)	2 (0.5)	6 (1.6)
Other	1 (0.4)	4 (1.6)	3 (1.2)	3 (1.2)	0	0	0	0	0	0	3 (0.8)	3 (0.8)
Unknown	0	0	0	0	0	0	2 (3.0)	2 (3.0)	2 (1.6)	2 (1.6)	2 (0.5)	2 (0.5)

SCS = Summary of Clinical Safety (cut-off 09 May 2014)
Safety update data cut-off date: 19 September 2014

Table 63: Grade 5 Adverse Events (Fatal) Reported in Study GO28141 (Safety Population)

	Placebo + Vemurafenib		Cobimetinib + Vemurafenib	
	SCS n=239	safety update n=246	SCS n=254	safety update n=247
Patient experiencing event, n (%)				
Any AE	3 (1.3)	3 (1.2) [a]	6 (2.4)	5 (2.0) [b]
General disorders and administration site conditions				
-Overall-	1 (0.4)	0	2 (0.8)	1 (0.4)
Fatigue	1 (0.4) [c]	0	1 (0.4)	0
Asthenia	0	0	1 (0.4)	0
Death	0	0	1 (0.4)	1 (0.4)
Cardiac disorders				
-Overall-	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Cardiac arrest	0	0	1 (0.4)	1 (0.4)
Cardiac failure	1 (0.4)	1 (0.4)	0	0
Nervous system disorders				
-Overall-	0	0	2 (0.8)	1 (0.4)
Cerebral hemorrhage	0	0	1 (0.4)	0
Hemiparesis	0	0	1 (0.4)	0
Coma	0	0	0	1 (0.4)
Infections and infestations				
-Overall-	0	0	1 (0.4)	2 (0.8)
Clostridium difficile colitis	0	0	0	1 (0.4)
Pneumonia	0	0	1 (0.4)	1 (0.4)
Respiratory, thoracic and mediastinal disorders				
-Overall-	1 (0.4)	2 (0.8)	0	0
Atelectasis	0	1 (0.4)	0	0
Pulmonary embolism	1 (0.4) [c]	1 (0.4) [c]	0	0

SCS = Summary of Clinical Safety (cut-off 09 May 2014)
Safety update data cut-off date: 19 September 2014

Laboratory findings

At the original data cut-off date (09 May 2014), in patients with normal alkaline phosphatase values at baseline, elevation of alkaline phosphatase above the normal range occurred 63.0 % vs. 44.6 % in the cobimetinib plus vemurafenib arm vs. the placebo arm, respectively; the proportion who had a worst grade of ≥ 3 during treatment was 15/248 (6%) in the cobimetinib plus vemurafenib arm and 7/232 (3%) in the placebo plus vemurafenib arm.

In patients with normal ALT values at baseline, elevation of ALT above the normal range occurred in more patients in the cobimetinib plus vemurafenib arm (63.4% vs. 50.5%); the proportion with a worst grade of ≥ 3 during treatment was 23/248 (9%) in the cobimetinib plus vemurafenib arm and 12/234 (5%) in the placebo plus vemurafenib arm.

Elevation of AST above the normal range occurred in a greater proportion of patients in the cobimetinib plus vemurafenib arm (66.8% vs. 41.3%); the proportion with a worst grade of ≥ 3 during treatment was 14/244 (5.7%) patients in the cobimetinib plus vemurafenib arm and 5/230 (2.2%) in the placebo plus vemurafenib arm.

In patients with normal bilirubin values at baseline, elevation of bilirubin above the normal range was less common in the cobimetinib plus vemurafenib arm (29.2%) than in the placebo plus vemurafenib

arm (40.5%); subjects with a worst grade of ≥ 3 were 5/249 (2%) in the cobimetinib plus vemurafenib arm and 2/234 (0.9%) in the placebo plus vemurafenib arm.

In patients with normal GGT levels at baseline, elevation of GGT above the normal range occurred with similar frequency in the two arms (48.8% and 47.7% in the cobimetinib plus vemurafenib arm and the placebo plus vemurafenib arm, respectively); the proportion with a worst grade of ≥ 3 during treatment was 47/244 (19.2%) and 36/227 (15.8%) patients in the respective arms.

For patients with normal CPK values at baseline, elevations of CPK above the normal range occurred in a greater proportion of patients in the cobimetinib plus vemurafenib arm (64.8%) than in the placebo plus vemurafenib arm (9.9%).

Reductions of lymphocytes below the normal range at some time during the study occurred in 55.6% of patients in the cobimetinib plus vemurafenib arm and 35.0% in the placebo plus vemurafenib arm; events of Grade ≥ 3 occurred in 18/191 (9.4%) and 11/175 (6.2%) of patients in the respective arms. Reductions in neutrophils occurred 6.4% on the cobimetinib plus vemurafenib arm and 7.9% in the control arm.

In patients with normal creatinine levels at baseline, elevation of creatinine above normal range occurred in 45.3% of subjects in the cobimetinib plus vemurafenib arm and 42.5% in the placebo plus vemurafenib arm: grade 3 elevations occurred in 7/250 (2.8%) and 2/236 (0.8%) patients in the respective arms. There were no Grade 4 elevations of creatinine.

Mean changes from baseline for QTcF at the Cycle 6 assessment ranged from 13.0 ms in the cobimetinib plus vemurafenib arm to 14.0 ms in the placebo plus vemurafenib arm. The maximum change from baseline QTcF exceeded 60 ms for 6 patients (2.4%) in the cobimetinib plus vemurafenib arm and 1 patient (0.4%) in the placebo plus vemurafenib arm. QTcF prolongation of > 500 ms occurred in 4 patients (1.6%) and in 1 patient (0.4%) in the respective arms. None of the patients with a mean QTcF value > 500 ms at any post-baseline assessment or with a maximum change in mean QTcF value > 60 ms from baseline at any post-baseline assessment had a reported adverse event of QTc prolongation Grade ≥ 3. Based on the criteria listed in the NCI CTCAE version 4 for ECG QT prolongation, the incidence of patients with Grade 1 – 3 ECG QT prolongation was: for Grade 1 (QTcF 450 – 480 ms), 30 patients (11.8%) in the cobimetinib plus vemurafenib arm and 20 (8.4%) in the placebo plus vemurafenib arm; for Grade 2 (QTcF 481 – 500 ms), 3 patients (0.8%) in the cobimetinib plus vemurafenib arm and 6 (2.5%) in the placebo plus vemurafenib arm; for Grade 3 QTcF (> 501 ms on at least two separate ECGs), 1 patient (0.4%) in the cobimetinib plus vemurafenib arm, no patients in the placebo plus vemurafenib arm.

Regarding the median LVEF values, the cobimetinib plus vemurafenib arm had a median decrease of 3% from baseline and no change was reported in the placebo plus vemurafenib arm. For 82.8% of patients in the cobimetinib plus vemurafenib arm and 88.7% of patients in the placebo plus vemurafenib arm, the worst change from baseline in LVEF value was < 10%. Of the patients in the cobimetinib plus vemurafenib arm who experienced a decrease from baseline of > 10%, the worst absolute value of LVEF remained ≥ 50% for 28 patients (11.7%). In addition, 4.2% of subjects in the cobimetinib plus vemurafenib arm experienced both a > 10% decrease from baseline and a worst absolute LVEF value < 50% vs. 1.7% of the placebo plus vemurafenib arm; no patient in the cobimetinib plus vemurafenib arm experienced a worst absolute LVEF value lower than 40% vs 2 patients of the placebo plus vemurafenib arm.

Safety in special populations

The incidences of adverse events (AEs) in age groups for selected categories of AEs in Study GO28141 are illustrated in Table 64.

Table 64: Incidence of AEs by Age Group in Study GO28141 (Safety Population)

Adverse Event categories, n (%)	Placebo + Vemurafenib n=239				Cobimetinib + Vemurafenib n=254			
	Age <65 n=172 (72.0)	Age 65-74 n=45 (18.8)	Age 75-84 n=21 (8.8)	Age 85+ n=1 (0.4)	Age <65 n=189 (74.4)	Age 65-74 n=44 (17.3)	Age 75-84 n=17 (6.7)	Age 85+ n=4 (1.6)
Total AEs	166 (96.5)	45 (100.0)	21 (100.0)	1 (100.0)	185 (97.9)	44 (100.0)	17 (100.0)	4 (100.0)
Serious AEs – Total*	34 (19.8)	19 (42.2)	7 (33.3)	0	45 (23.8)	22 (50.0)	7 (41.2)	1 (25.0)
- Fatal	0	3 (6.7)	0	0	3 (1.6)	2 (4.5)	0	1 (25.0)
- Hospitalization/prolong existing hospitalization	25 (14.5)	15 (33.3)	4 (19.0)	0	34 (18.0)	20 (45.5)	7 (41.2)	0
- Life-threatening	3 (1.7)	1 (2.2)	0	0	2 (1.1)	0	1 (5.9)	1 (25.0)
- Disability/incapacity	2 (1.2)	2 (4.4)	2 (9.5)	0	4 (2.1)	1 (2.3)	1 (5.9)	0
- Other (medically significant)	9 (5.2)	4 (8.9)	1 (4.8)	0	6 (3.2)	3 (6.8)	0	0
AE leading to drop-out**	17 (9.9)	12 (26.7)	4 (19.0)	0	22 (11.6)	13 (29.5)	6 (35.3)	1 (25.0)
Psychiatric disorders	23 (13.4)	12 (26.7)	3 (14.3)	0	28 (14.8)	6 (13.6)	2 (11.8)	0
Nervous system disorders	58 (33.7)	20 (44.4)	5 (23.8)	0	74 (39.2)	16 (36.4)	3 (17.6)	1 (25.0)
Accidents and injuries	31 (18.0)	11 (24.4)	3 (14.3)	0	33 (17.5)	4 (9.1)	1 (5.9)	0
Cardiac disorders	17 (9.9)	3 (6.7)	3 (14.3)	0	20 (10.6)	6 (13.6)	5 (29.4)	1 (25.0)
Vascular disorders	24 (14.0)	9 (20.0)	5 (23.8)	0	44 (23.3)	9 (20.5)	3 (17.6)	1 (25.0)
Cerebrovascular disorders	0	0	0	0	4 (2.1)	1 (2.3)	0	0
Infections and infestations	62 (36.0)	11 (24.4)	8 (38.1)	0	80 (42.3)	16 (36.4)	7 (41.2)	2 (50.0)
Anticholinergic syndrome	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	6 (3.5)	7 (15.6)	0	0	11 (5.8)	4 (9.1)	2 (11.8)	1 (25.0)

*An adverse event may be considered serious for multiple reasons. **Defined as AEs leading to discontinuation of cobimetinib or placebo. Source:

Safety related to drug-drug interactions and other interactions

A drug-drug interaction study (GP28620, a Phase 1, Open-Label Study) was conducted to investigate the effect of itraconazole (a potent CYP3A4 inhibitor) on cobimetinib pharmacokinetics in healthy subjects. The following cobimetinib PK parameters were altered with co-administration of itraconazole (QD oral dose of 200 mg itraconazole on Days 4 to 14) with cobimetinib (single dose oral administration of 10 mg): median tmax was delayed by 2 hours; t1/2 was prolonged from 54.1 to 118 hours; Cmax increased by 3.2-fold; AUC0-∞ increased by 6.6-fold (see pharmacology section).

Discontinuation due to adverse events

An overview of discontinuations due to adverse events and the list of events leading to discontinuations are reported in Table 65 and Table 66, respectively.

Table 65: Summary of patients who discontinued study treatment as a result of adverse events (Safety-Evaluable Population - cut-off 09 May 2014, Study GO28141)

Discontinuation from	Placebo + vemurafenib (n=239)	Cobimetinib + vemurafenib (n=254)	All Patients (n=493)
Cobimetinib or Placebo*	33 (13.8%)	42 (16.5%)	75 (15.2%)
Vemurafenib*	32 (13.4%)	35 (13.8%)	67 (13.6%)
Cobimetinib/Placebo and Vemurafenib	28 (11.7%)	32 (12.6%)	60 (12.2%)

* These rows indicate the numbers of patients discontinued from the indicated treatment, regardless of whether the other treatment was also discontinued.

Table 66: Summary of adverse events leading to permanent discontinuation of study treatment in at least 1% of patients in either arm in study GO28141 (Safety Population)

	Placebo + Vemurafenib		Cobimetinib + Vemurafenib	
	SCS n=239	safety update n=246	SCS n=254	safety update n=247
Patient experiencing event, n (%)				
Withdrawal of cobimetinib / placebo				
Increased AST	1 (0.4)	1 (0.4)	6 (2.4)	6 (2.4)
Increased GGT	3 (1.3)	3 (1.2)	3 (1.2)	4 (1.6)
Increased ALT	1 (0.4)	1 (0.4)	4 (1.6)	4 (1.6)
Rash	1 (0.4)	1 (0.4)	4 (1.6)	4 (1.6)
Retinal detachment	0	0	5 (2.0)	5 (2.0)
Pyrexia	0	0	3 (1.2)	3 (1.2)
Withdrawal of vemurafenib				
Increased ALT	3 (1.3)	3 (1.2)	5 (2.0)	5 (2.0)
Increased AST	2 (0.8)	2 (0.8)	6 (2.4)	6 (2.4)
Increased GGT	4 (1.7)	4 (1.6)	4 (1.6)	5 (2.0)
Rash	1 (0.4)	1 (0.4)	4 (1.6)	4 (1.6)
Pyrexia	1 (0.4)	1 (0.4)	3 (1.2)	3 (1.2)
Retinal Detachment	0	0	3 (1.2)	3 (1.2)
Withdrawal of cobimetinib / placebo and vemurafenib				
Increased AST	1 (0.4)	1 (0.4)	5 (2.0)	5 (2.0)
Increased GGT	3 (1.3)	3 (1.2)	3 (1.2)	4 (1.6)
Increased ALT	1 (0.4)	1 (0.4)	4 (1.6)	4 (1.6)
Rash	1 (0.4)	1 (0.4)	4 (1.6)	4 (1.6)
Pyrexia	0	0	3 (1.2)	3 (1.2)
Retinal detachment	0	0	3 (1.2)	3 (1.2)

AE = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; SCS = Summary of Clinical Safety.

SCS = Summary of Clinical Safety (cut-off 09 May 2014)
Safety update data cut-off date: 19 September 2014

Dose interruptions/reductions and the most frequent AEs leading to dose modification are summarised in Table 67 and Table 68, respectively.

Table 67: Summary of patients who had dose interruptions or reductions of study treatment as a result of adverse events (Safety-Evaluable Population – cut-off 19 September 2014, Study GO28141)

Dose Interruption or Reduction of	Placebo + Vemurafenib (n=246)	Cobimetinib + Vemurafenib (n=247)	All Patients (n=493)
Cobimetinib or Placebo	91 (37.0%)	135 (54.7%)	226 (45.8%)
Vemurafenib	121 (49.2%)	144 (58.3%)	265 (53.8%)
Cobimetinib/Placebo and Vemurafenib	87 (35.4%)	110 (44.5%)	197 (40.0%)

Table 68: Summary of most frequent AEs (in ≥ 5% of patients) leading to dose modification of cobimetinib, vemurafenib, or both study drugs (cut-off 19 September 2014, Study GO28141)

Drug modified	Cobimetinib	Vemurafenib	Both Drugs[a]
Adverse Events	Rash[b] (13.4%) Serous Retinopathy[b] (10.2%) Diarrhea (8.7%) Pyrexia (5.9%) Vomiting (5.1%) Nausea (5.1%) Increased Blood CPK (5.1%)	Rash[b] (16.5%) Increased ALT (9.8%) Diarrhea (9.1%) Pyrexia (7.5%) Increased AST (7.5%) Increased GGT (7.1%) Vomiting (6.3%) Nausea (5.5%)	Rash[b] (11.4%) Serous Retinopathy[b] (8.7%) Diarrhea (7.9%) Pyrexia (5.9%) Vomiting (5.1%)

[a] Denotes group term

[b] Patients with modification of both drugs are also represented in the columns for modification of each individual drug

Post marketing experience

The applicant did not submit post-marketing data as the product had not yet been approved.

2.6.1. Discussion on clinical safety

Safety assessment of cobimetinib in combination with vemurafenib is based on 376 patients from 2 studies, i.e. the phase Ib NO25395 (n=129) and the phase III GO28141 (n=247) studies. In the updated safety report (submitted as an Appendix to Response to Q 56, D120 LoQ), mean/median exposure to cobimetinib in the 2 studies was 313/211 days (NO25395) and 243/267 days (GO28141). Mean exposure in the phase 1 MEK4592 cobimetinib monotherapy study was ~2 months (67 days).

In the original report, the most common AEs that occurred with higher frequency in the cobimetinib plus vemurafenib arm, compared with the placebo plus vemurafenib arm, include diarrhoea (56.7% vs. 28.0%), nausea (39.0% vs. 23.8%), blood creatine phosphokinase increased (29.9% vs. 2.9%), photosensitivity reaction (28.3% vs. 15.9%), aspartate aminotransferase (AST) increased (22.0% vs.

12.6%), and vomiting (21.3% vs. 12.1%). This pattern was unchanged in the Safety Update Report, although the incidences were now somewhat higher (probably due to the longer exposure).

Common AEs that occurred with higher frequency in the placebo plus vemurafenib arm than in the cobimetinib plus vemurafenib arm include arthralgia (40.2% vs. 32.7%), alopecia (29.3% vs. 13.8%), and hyperkeratosis (28.5% vs. 10.2%).

In the cobimetinib monotherapy study MEK4592g the most frequent AEs among all subjects were diarrhoea (67.0%), fatigue (50.4%), rash (49.6%), nausea, vomiting (33.9% each), oedema peripheral (28.7%), abdominal pain (24%) and constipation (21%).

The temporal pattern in relation to treatment start of the most common AEs and grade ≥3 AEs in the two arms of study GO28141 and the BRAFi-naïve patients in study NO25395 was further analysed.

The majority of common AEs and Grade ≥3 AEs reported in BRAFi-naïve patients dosing with cobimetinib plus vemurafenib in the GO28141 and NO25395 studies had highest incidence in the first 1 – 3 Cycles on treatment and decreased to low levels thereafter. This patterns was seen in diarrhoea, nausea and vomiting, serous retinopathy/retinal detachment, photosensitivity, blood creatinine phosphokinase (CPK) increased, ALT increased, AST increased, pyrexia, rash, arthralgia, and fatigue. In most of the AEs (underlined), the increase in incidence during early cycles was clearly more pronounced in the cobimetinib + vemurafenib arm compared to the placebo + vemurafenib arm, and a similar pattern was found in BRAFi-naïve patients in study NO25395. Cases of serous retinopathy have been reported in patients treated with Cotellic (see section 4.4.) For patients reporting new or worsening visual disturbances, an ophthalmologic examination is recommended. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation (see Table 1 in section 4.2) (SmPC section 4.8). Therefore ocular events related to serous retinopathy (e.g. retinal detachment) have been included in the RMP as an important identified risk. The safety risk in patients with pre-existing retinal pathology or risk factors for retinal vein occlusion has been described as missing information. The risk will be monitored through PSURs and a recommendation was highlighted in the PL for patients to discuss with their HCP if they have eye problems. Diarrhoea has also been included as an important identified risk and will be managed through a warning included in section 4.4. Cases of Grade ≥3 and serious diarrhoea have been reported in patients treated with Cotellic. Diarrhoea should be managed with antidiarrhoeal agents and supportive care. For Grade ≥3 diarrhoea that occurs despite supportive care, Cotellic and vemurafenib should be withheld until diarrhoea has improved to Grade ≤1. If Grade ≥3 diarrhoea recurs, the dose of Cotellic and vemurafenib should be reduced (see section 4.2).

Bleeding events have been reported more frequently in the Cotellic plus vemurafenib arm than in the placebo plus vemurafenib arm (all types and Grades: 10% vs 6%). Higher frequencies in the Cotellic plus vemurafenib arm were observed for cerebral haemorrhage (1% vs 0%), gastrointestinal tract haemorrhage (3% vs 1%), reproductive system haemorrhage (2% vs 1%) and haematuria (2% vs 1%). The majority of events were Grade 1 or 2 and non-serious (9% of patients in the Cotellic plus vemurafenib arm vs 5% patients in the placebo plus vemurafenib arm). Grade 3-5 events were experienced by 1% and 0.4% of patients, respectively. The median time to first onset was 2.8 months (range 0.0 to 12.7 months) in the Cotellic plus vemurafenib arm (SmPC section 4.8).

No clear temporal pattern was seen for the common AEs alopecia, Gamma-Glutamyl Transferase (GGT) Increased, Squamous cell carcinoma (SCC) of skin, Keratoacanthoma (KA) and Hyperkeratosis. These AEs, with the notable exception of Gamma-Glutamyl Transferase (GGT) Increased, were clearly more common in the placebo + vemurafenib arm in study GO28141.

In the originally submitted data, the most common Grade ≥ 3 AEs that occurred at higher frequency (≥ 2% difference) in patients treated with cobimetinib plus vemurafenib, compared with patients treated with placebo plus vemurafenib, were, respectively, ALT increased (11.4% vs. 6.3% of patients), blood creatine phosphokinase increased (10.2% vs. 0%), AST increased (8.3% v 2.1%), diarrhoea (6.3% vs. 0%), blood alkaline phosphatase increased (4.3% vs. 1.7%), hyponatremia (2.4% vs. 0.4%), photosensitivity reaction (2.4% vs. 0%), and retinal detachment (2.4% vs. 0%). Liver laboratory abnormalities, specifically ALT, AST, and ALP have been observed in patients treated with Cotellic in combination with vemurafenib (see section 4.4). Liver laboratory tests should be monitored before initiation of combination treatment and monthly during treatment, or more frequently if clinically indicated (see section 4.2). Photosensitivity has been observed with a higher frequency in the Cotellic plus vemurafenib vs placebo plus vemurafenib arm (41% vs 31%). The majority of events were Grades 1 or 2, with Grade ≥3 events occurring in 3% of patients in the Cotellic plus vemurafenib arm vs 0% in the placebo plus vemurafenib arm. There were no apparent trends in the time of onset of Grade ≥3 events. Grade ≥3 photosensitivity events in the Cotellic plus vemurafenib arm were treated with primary topical medicinal products in conjunction with dose interruptions of both cobimetinib and vemurafenib (see section 4.2). No evidence of phototoxicity was observed with Cotellic as a single agent (SmPC section 4.8). Therefore, photosensitivity has been included in the RMP as an important identified risk.

Decrease in LVEF from baseline has been reported in patients receiving Cotellic (see section 4.4). LVEF should be evaluated before initiation of treatment to establish baseline values, then after the first month of treatment and at least every 3 months or as clinically indicated until treatment discontinuation. Decrease in LVEF from baseline can be managed using treatment interruption, dose reduction or with treatment discontinuation (see section 4.2) (SmPC section 4.8). Therefore, left ventricular dysfunction (including decreased LVEF and cardiomyopathy) has been included in the RMP as an important identified risk.

The most common Grade ≥ 3 AEs that occurred at a higher frequency in patients treated with placebo plus vemurafenib, compared with patients treated with cobimetinib plus vemurafenib, were, respectively, squamous cell carcinoma of the skin (11.3% vs. 2.4%), keratoacanthoma (7.5% vs. 0.8%), arthralgia (5.0% vs. 2.4%), myalgia (2.5% vs. 0.4%), and hyperkeratosis (2.1% vs. 0%). Cutaneous squamous cell carcinoma has been reported with a lower frequency in the Cotellic plus vemurafenib vs placebo plus vemurafenib arm (all Grade: 3% vs 11%). Keratoacanthoma has been reported with a lower frequency in the Cotellic plus vemurafenib vs placebo plus vemurafenib arm (all Grade: 1% vs 8%). Hyperkeratosis has been reported with a lower frequency in the Cotellic plus vemurafenib vs placebo plus vemurafenib arm (all Grade: 10% vs 29%) (SmPC section 4.8).

These patterns were largely unchanged in the Safety Update Report, with the exception of grade ≥3 hypertension, increased blood ALP, and BCC, where the incidence in the cobimetinib + vemurafenib arm were now ≥2 % higher than in the placebo arm.

A significant difference in the incidence of elevated Blood Creatine Phosphokinase Increased between the two treatment arms in study GO28141. There were 2 cases of rhabdomyolysis observed in study GO28141 (1 in each treatment arm) and no cases were reported in Study NO25395. Asymptomatic increases in blood CPK levels were observed with a higher frequency in the Cotellic plus vemurafenib arm vs placebo plus vemurafenib arm in Study GO28141 (see section 4.2). One event of rhabdomyolysis was observed in each treatment arm of the Study with concurrent increases in blood CPK (SmPC section 4.8). Therefore, rhabdomyolysis has been included as an important potential risk in the RMP.

The table below provides the frequency of measured liver laboratory abnormalities and elevated creatine phosphokinase for all Grades and Grades 3-4.

Liver and other laboratory tests observed in the phase III Study GO28141

Changes in reported laboratory data	Cobimetinib plus Vemurafenib (n = 254) (%)		Placebo plus Vemurafenib (n = 239) (%)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Liver function test				
Increased ALP	69	7	54	3
Increased ALT	66	10	53	6
Increased AST	69	7	42	2
Increased GGT	60	19	59	17
Increased blood bilirubin	33	2	43	1
Other laboratory abnormalities				
Increased blood CPK	65	11	13	<1

The majority of deaths were due to PD and there were no patterns with respect to the type of Grade 5 events reported, and for majority of these events, the patient's underlying disease was considered to contribute to the cause of the event.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (SmPC section 4.3). Cotellic has minor influence on the ability to drive or use machines. Visual disturbances have been reported in some patients treated with cobimetinib during clinical trials (see sections 4.4 and 4.8). Patients should be advised not to drive or use machines if they experience visual disturbances or any other adverse effects that may affect their ability (SmPC section 4.7).

The majority of patients in Study GO28141 were below 65 years of age. Patients aged 65-74, 75-84, and 85+ accounted for 17.3%, 6.7%, and 1.6% of patients, respectively in the cobimetinib plus vemurafenib arm, and 18.8%, 8.8%, and 0.4%, respectively in the placebo plus vemurafenib arm. Thus there were small sample sizes in each subgroup. In general, safety findings were consistent with the findings reported in the GO28141 CSR for the overall study population but the frequencies of serious AEs in both study arms were higher among older patients (above 65 years). Frequencies of AEs leading to discontinuation of cobimetinib/placebo, hospitalization, and Sum of the [incidence of] AEs postural hypotension, falls, black outs, syncope, dizziness, ataxia, and fractures were also higher in cobimetinib-treated older patients than in age-matched patients in the control arm. In addition, a numerically greater percentage of patients aged 65-74 and 75-84, compared to patients below 65 years of age, reported a clinically meaningful decrease in global health status, in the cobimetinib plus vemurafenib arm. In the placebo plus vemurafenib arm, there were no trends in decrease in global health status by age group. Thus, although the experience in patients ≥65 years is limited, tolerability seems to be more restricted in this age group. In the Phase III study with Cotellic in combination with vemurafenib in patients with unresectable or metastatic melanoma (n=254), 189 patients (74%) were <65 years of age, and 44 patients (17%) were age 65-74 years of age, 17 (7%) were 75-84 years of age, and 4 patients (2%) were aged ≥85 years The proportion of patients experiencing adverse events (AE) was similar in the patients aged <65 years and those aged ≥65 years. Patients ≥65 years were more likely to experience serious adverse events (SAEs) and experience AEs leading to discontinuation of cobimetinib than those <65 years (SmPC section 4.8).

Based on the results from population PK analysis, exposure-response analysis for efficacy and safety, and physiologically-based PK simulations, cobimetinib may be administered with mild CYP3A inhibitors

without any dose adjustment. Caution should be exercised when cobimetinib is administered with moderate inhibitors or inducers of CYP3A. Co-administration of strong inhibitors or strong inducers with cobimetinib should be avoided.

No pharmacokinetic trial in subjects with renal impairment has been conducted. Dose adjustment is not recommended for mild to moderate renal impairment based on the results of the population pharmacokinetic analysis. There are minimal data for Cotellic in patients with severe renal impairment. Cotellic should be used with caution in patients with severe renal impairment (SmPC section 4.8).

No pharmacokinetic data in subjects with hepatic impairment are available (SmPC section 4.8). Thus, the CHMP has requested that the applicant submits the results of study GP29342, a Phase I, open label, single-dose study to evaluate the pharmacokinetics and safety of cobimetinib in subjects with mild, moderate or severe hepatic impairment compared to healthy subjects.

The safety and efficacy of Cotellic in non-Caucasian patients have not been established (SmPC section 4.2).

There are no data from the use of Cotellic in pregnant women. Studies in animals have shown embryolethality and foetal malformations of the great vessel and skull (see section 5.3). Cotellic should not be used during pregnancy unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the foetus (SmPC section 4.6). It is not known whether cobimetinib is excreted in human breast milk. A risk to the newborns/infants cannot be excluded. A decision should be made whether to discontinue breast-feeding or discontinue Cotellic therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman (SmPC section 4.6). There are no data in humans for cobimetinib. In animals, no fertility studies have been performed, but adverse effects were seen on female reproductive organs (see section 5.3). The clinical relevance of this is unknown (SmPC section 4.6). The use of the cobimetinib and vemurafenib in pregnancy and lactation has been included as missing information in the RMP.

Discontinuations for adverse events (AEs) in Study GO28141, and AEs leading to dose interruptions and reductions in both studies GO28141 and NO25395, had highest incidence in the first 1-3 cycles and were of lower frequency thereafter. The discontinuation rates for AE for both study treatments, were higher for the cobimetinib plus vemurafenib arm (15.0%) than for the vemurafenib plus placebo arm (8.1%), compared with discontinuation rates of 12.6% and 11.7%, respectively. Likewise, the frequency of dose modification or interruption of cobimetinib or placebo, of vemurafenib, or of both drugs in the respective regimens was higher in the cobimetinib plus vemurafenib arm (54.7%, 58.3%, 44.5%, respectively) than in the placebo plus vemurafenib arm (37.0%, 49.2%, 35.4%, respectively). In study NO25395 among the BRAFi-naïve patients (at the safety update), the frequencies of AEs leading to reduction or interruption of cobimetinib, of vemurafenib, or of both study drugs were 63.5%, 76.2% and 60.3%, respectively.

The rather high frequency of discontinuations and the remarkably high rate of dose interruptions/reductions due to AEs clearly indicate a limited tolerability of cobimetinib in combination with vemurafenib. The nature of the AEs that led to either drug interruptions/dose reductions or drug discontinuations appear to be largely overlapping in preferred terms/SOC and also showed a preference to occur during the early treatment cycles. Although most of these AEs were reversible and could be clinically managed, i.e. by dose interruption, dose reductions, and standard clinical measures, close monitoring during especially early cycles and in certain sub-groups, e.g. elderly, seems to be justified.

The decision on whether to reduce the dose for either or both treatments should be based on the prescriber's assessment of individual patient safety or tolerability. Dose modification of Cotellic is

independent of vemurafenib dose modification. If doses are omitted for toxicity, these doses should not be replaced (SmPC section 4.2). Once the dose has been reduced, it should not be increased at a later time. Table 1 in the SmPC section 4.2 gives general Cotellic dose modification guidance (SmPC section 4.2).

Permanent discontinuation of Cotellic treatment should be considered if cardiac symptoms are attributed to Cotellic and do not improve after temporary interruption (SmPC section 4.2). Table 2 of the SmPC provides recommendation on dose modifications for Cotellic in patients with left ventricular ejection fraction (LVEF) decrease from baseline (SmPC section 4.2). The risk of safety in patients with cardiac impairment (including congestive heart failure, current unstable angina, or left ventricular ejection fraction < 50%) has been included in the RMP as missing information. The risk will be managed through recommendations for dose reduction and treatment discontinuation guidance for left ventricular dysfunction as described in section 4.2 (Posology and method of administration) and a warning has been included in section 4.4.

Vemurafenib treatment can be continued when Cotellic treatment is modified, if clinically indicated (SmPC section 4.2).

Dose modification advice for Cotellic when used with vemurafenib (SmPC section 4.2)

Liver laboratory abnormalities

For Grade 1 and 2 liver laboratory abnormalities, Cotellic and vemurafenib should be continued at the prescribed dose.

Grade 3: Cotellic should be continued at the prescribed dose. The dose of vemurafenib may be reduced as clinically appropriate. Please refer to the vemurafenib SmPC.

Grade 4:

Cotellic treatment and vemurafenib treatment should be interrupted. If liver laboratory abnormalities improve to Grade ≤1 within 4 weeks, Cotellic should be restarted at a dose reduced by 20 mg and vemurafenib at a clinically appropriate dose, per its SmPC.

Cotellic treatment and vemurafenib treatment should be discontinued if liver laboratory abnormalities do not resolve to Grade ≤1 within 4 weeks or if Grade 4 liver laboratory abnormalities recur after initial improvement.

Creatine phosphokinase (CPK) elevations

Cotellic dosing does not need to be modified or interrupted to manage asymptomatic CPK elevations.

Photosensitivity

Grade ≤2 (tolerable) photosensitivity should be managed with supportive care.

Grade 2 (intolerable) or Grade ≥3 photosensitivity: Cotellic and vemurafenib should be interrupted until resolution to Grade ≤1. Treatment can be restarted with no change in Cotellic dose. Vemurafenib dosing should be reduced as clinically appropriate, please refer to its SmPC for further information.

Rash

Rash events may occur with either Cotellic or vemurafenib treatment. The dose of Cotellic and/or vemurafenib may be either temporarily interrupted and/or reduced as clinically indicated.

Additionally, for:

– Grade ≤2 (tolerable) rash should be managed with supportive care. Cotellic dosing can be continued without modification.

– Grade 2 (intolerable) or Grade ≥3 acneiform rash: General dose modification recommendations in Table 1 for Cotellic should be followed. Vemurafenib dosing can be continued when Cotellic treatment is modified (if clinically indicated).

– Grade 2 (intolerable) or Grade ≥3 non-acneiform or maculopapular rash: Cotellic dosing can be continued without modification if clinically indicated. Vemurafenib dosing may be either temporarily interrupted and/or reduced, please refer to its SmPC for further information.

There is no experience with overdose in human clinical trials. In case of suspected overdose, cobimetinib should be withheld and supportive care instituted. There is no specific antidote for overdosage with cobimetinib (SmPC section 4.8).

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

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V (SmPC section 4.8).

Long-term safety has been identified as missing information in the RMP. The safety will be monitored through regular PSURs.

2.6.2. Conclusions on the clinical safety

The safety assessment of cobimetinib in metastatic melanoma rests mainly upon clinical data on 376 patients subjected to combined treatment with vemurafenib and cobimetinib. Common side effects encountered in the studies are e.g. diarrhoea, rash, nausea/vomiting, fatigue, arthralgia, pyrexia, photosensitivity reactions. Elevations of laboratory parameters e.g. LFT (ALT, AST, GGT, ALP) and blood creatine phosphokinase are also very often seen. While many of these occur frequently during monotherapy with vemurafenib, the net effect of the addition of cobimetinib varies between an increase (e.g. for diarrhoea, nausea, and photosensitivity reactions) and a decrease in frequency (e.g. for arthralgia, hyperkeratosis, and alopecia). In a few cases, e.g. ocular events, grade ≥3 photosensitivity reactions, elevation in blood creatine phosphokinase, the AE seems preferentially associated with cobimetinib.

There appears to be an increased incidence of ADRs in the first 1 – 3 cycles on treatment compared to later cycles. This pattern was observed in diarrhoea, nausea and vomiting, serous retinopathy/retinal detachment, photosensitivity, blood creatinine phosphokinase (CPK) increased, ALT increased, AST increased, pyrexia, rash, arthralgia, and fatigue. The frequent discontinuations (almost 20 % in the cobimetinib + vemurafenib arm) discontinued at least one study drug due to AEs) and very frequent dose interruptions/reductions (≥60 % interrupted dose or reduced the dose of at least 1 study drug) in the pivotal study GO28141, reflected this temporal pattern of the incidence of ADRs. Reduced doses of cobimetinib or vemurafenib may have contributed to the decreased incidence of AEs in later treatment cycles. Thus, close monitoring of patients and implementation of dose interruptions/reductions is included as recommendations in section 4.2 of the SmPC.

In conclusion, safety and tolerability of cobimetinib in combination with vemurafenib for the treatment of patients with advanced or metastatic melanoma appears acceptable and clinically manageable.

The CHMP considers the following measures necessary to address issues related to safety:

- GP29342: A Phase I, open label, single-dose study to evaluate the pharmacokinetics and safety of cobimetinib in subjects with mild, moderate or severe hepatic impairment compared to healthy subjects: safety in subjects with hepatic impairment

2.7. Risk Management Plan

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

The PRAC considered that the risk management plan version 1.2 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC advice.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and/or CHMP.

The CHMP endorsed the Risk Management Plan version 1.3 with the following content:

Safety concerns

Table 69: Safety concerns

Summary of safety concerns	
Important identified risks	Ocular events related to serous retinopathy (e.g. retinal detachment) Left ventricular dysfunction (including decreased LVEF and cardiomyopathy) Photosensitivity Diarrhea Pneumonitis
Important potential risks	Rhabdomyolysis Serious hepatotoxicity Impaired female fertility Teratogenicity and developmental toxicity
Missing information	Long-term safety Safety in patients with moderate and severe hepatic impairment Safety in patients with cardiac impairment (including congestive heart failure, current unstable angina, or left ventricular ejection fraction < 50%) Safety in patients with pre-existing retinal pathology or risk factors for retinal vein occlusion Safety and long-term efficacy in patients with CNS involvement Drug-drug interactions (with CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYPC19 and CYP2D6) Use in patients < 18 years of age Use in pregnancy and lactation

Pharmacovigilance plan

Table 70: Pharmacovigilance plan

Activity / Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports (planned or actual)**
GP29342: A Phase I, open label, single-dose study to evaluate the pharmacokinetics and safety of cobimetinib in subjects with mild, moderate or severe hepatic impairment compared to healthy subjects. (3)	To evaluate cobimetinib PK and safety in subjects with hepatic impairment	Use in patients with hepatic impairment	Ongoing	Estimated Final CSR: By Q4 2015
Pediatric Investigation Plan (PIP) EMEA-001425-PIP01-13-M01 Two pediatric studies in patients 6 months to 18 years of age (3)	<u>First Study (GO29665):</u> safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy dose finding study. <u>Second Study:</u> Confirmatory safety and efficacy trial in patients 6 months to < 18 years of age	Use in Patients 6 months to < 18 years of age	PIP agreed on December 2013 with modification on 16 May 2014	First Study start date by Q1 2016 Second Study start date by June 2021 Final CSRs to be available 6 months after each study completion
Study ML29155: Phase 2 Study of Cobimetinib in Combination with Vemurafenib in Active Melanoma Brain Metastases (coBRIM-B) (3)	A clinical Phase II study to determine the safety and efficacy of cobimetinib in combination with vemurafenib in patients with active melanoma brain metastases	Safety and efficacy in patients with CNS involvement	Ongoing	Estimated Final CSR: By Q4 2019
In vitro CYP time-dependent inhibition	An in vitro study to determine if	Drug-drug interactions with	Ongoing	Estimated Final Report: By Q4

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
study (15-1983) (3)	cobimetinib is a time-dependent inhibitor of CYP genes is ongoing	CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6		2015

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Risk minimisation measures

Table 71: Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Ocular events related *to* serous retinopathy (e.g. retinal detachment)	*SmPC:* *Dose reduction and treatment discontinuation guidance is described Table 1 in Section 4.2.* *Described in Section 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects): Patients should be assessed at each visit for symptoms of new or worsening visual disturbances. If symptoms of new or worsening visual disturbances are identified, an ophthalmologic examination is recommended. If serous retinopathy is diagnosed, Cotellic treatment should be withheld until visual symptoms improve to Grade ⩽1. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation (see Table 1 in Section 4.2).* *PL:* *Sections 2 and 4 recommend telling the doctor straight away if the patient experiences changes in vision.*	*None proposed*
Left ventricular dysfunction (including decreased LVEF and cardiomyopathy)	*SmPC:* *Dose reduction and treatment discontinuation guidance is described in Section 4.2 (Posology and method of administration).* *Described in Section 4.4 (Special warnings and precautions for use): LVEF should be evaluated before initiation of treatment to establish baseline values, then*	*None proposed*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	after the first month of treatment and at least every 3 months or as clinically indicated until treatment discontinuation. Decrease in LVEF from baseline can be managed using treatment interruption, dose reduction or with treatment discontinuation (see section 4.2). *Described as a selected ADR in section 4.8 (Undesirable effects) and Ejection fraction decreased is listed as a common ADR in Table 3 of Section 4.8.* *PL:* *Sections 2 and 4 recommend telling the doctor straight away if the patient experiences symptoms associated with heart problems***.**	
Photosensitivity	*SmPC:* *Dose reduction and treatment discontinuation guidance is described in Section 4.2 (Posology and method of administration).* *Described as a selected ADR in Section 4.8 (Undesirable effects)* *PL:* *Section 4 recommends telling the doctor straight away if the patient experiences increased skin sensitivity to sunlight.*	*None proposed*
Diarrhea	*SmPC:* *Dose reduction guidance is provided in Section 4.2* *Described in Section 4.4 (Special warnings and precautions for use): Diarrhoea should be*	*None proposed*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	managed with antidiarrhoeal agents and supportive care. For Grade ⩾ 3 diarrhoea that occurs despite supportive care, cobimetinib and vemurafenib should be withheld until diarrhoea has improved to Grade ⩽ 1. If Grade ⩾ 3 diarrhoea recurs, the dose of cobimetinib and vemurafenib should be reduced (see section 4.2). *Listed as a very common ADR in Table 3 of Section 4.8 (Undesirable effects).* *PL:* *Sections 2 and 4 recommend telling the doctor straight away if the patient experiences diarrhoea and following the doctor's instructions to help prevent or treat diarrhoea***.**	
Pneumonitis	*SmPC:* *Listed as a common ADR in Section 4.8 (Undesirable effects)* *PL:* *Listed as a common side effect in Section 4 (Possible side effects)*	*None proposed*
Rhabdomyolysis	*SmPC:* *Section 4.2 (Posology and method of administration): dosing does not need to be modified or interrupted to manage asymptomatic CPK elevations.* *Described in Section 4.8 (Undesirable effects):* *Asymptomatic increases in blood CPK levels were observed with a*	*None proposed*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	higher frequency in the Cotellic plus vemurafenib arm vs. placebo plus vemurafenib arm in Study GO28141 (see section 4.2).	
Serious hepatotoxicity	*SmPC:* *Dose reduction and treatment discontinuation guidance is described in Section 4.2 (Posology and method of administration).* *Described in Section 4.4 (Special warnings and precautions for use):* *Liver laboratory abnormalities, specifically increases in ALT, AST, and Alkaline Phosphatase* *(ALP), have been observed in patients treated with Cotellic plus vemurafenib (see Section 4.8).* *Liver value abnormalities should be monitored by liver laboratory tests before initiation of combination treatment and monthly during treatment, or more frequently as clinically indicated (see section 4.2).* *Grade 3 liver laboratory abnormalities should be managed with vemurafenib treatment interruption or dose reduction. Manage Grade 4 liver laboratory abnormalities with treatment interruption, dose reduction or with treatment discontinuation of both Cotellic and vemurafenib (see section 4.2).* *Described in Section 4.8 (Undesirable effects):*	*None proposed*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Liver laboratory tests should be monitored before initiation of combination treatment and monthly during treatment, or more frequently if clinically indicated (see Section 4.2). *Table 4 provides the frequency of measured liver laboratory abnormalities and elevated creatine phosphokinase for all Grades and Grades 3-4.*	
Impaired female fertility	*SmPC:* *Contraceptive methods are described in Section 4.6 (Fertility, pregnancy and lactation): Women of childbearing potential should be advised to use two effective contraceptive methods, such as a condom or other barrier method (with spermicide, if available) during treatment with Cotellic and for at least three months following treatment discontinuation.* *Preclinical data are described in Section 5.3 (Preclinical safety data).* *PL:* *Section 2 instructs women of childbearing potential to use two effective methods of contraception and to tell the doctor straight away if the patient becomes pregnant during treatment with Cotellic or within 3 months after the last dose. It also recommends asking the doctor or pharmacist for advice if the patient could be or plans to become pregnant.*	*None proposed*
Teratogenicity and	*SmPC:*	*None proposed*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
developmental toxicity	*Contraceptive methods are described in Section 4.6 (Fertility, pregnancy and lactation): Women of childbearing potential should be advised to use two effective contraceptive methods, such as a condom or other barrier method (with spermicide, if available) during treatment with Cotellic and for at least three months following treatment discontinuation.* *Section 4.6 also states that Cotellic should not be used during pregnancy unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the foetus.* *Preclinical data are described in Section 5.3 (Preclinical safety data).* *PL:* *Section 2 instructs women of childbearing potential to use two effective methods of* *contraception and to tell the doctor straight away* *if the patient is pregnant, becomes pregnant during treatment with Cotellic, or becomes pregnant within 3 months after the last dose.* *Section 2 states that Cotellic is not recommended during pregnancy and may cause permanent harm or birth defects to an unborn baby. The section also recommends asking the doctor or pharmacist for advice if the patient could be or plans*	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	to become pregnant.	
Long-term safety	*SmPC: None*	*None proposed*
Safety in patients with moderate and severe hepatic impairment	*SmPC:* *Dose reduction and treatment discontinuation guidance for hepatic impairment and liver* *laboratory abnormalities are described in Section 4.2 (Posology and method of administration).* *Section 5.2 (Pharmacokinetic properties): No pharmacokinetic data in subjects with hepatic impairment are available.* *PL:* *Section 2 recommends talking to the doctor, pharmacist, or nurse before taking Cotellic if the patient has liver problems.*	*None proposed*
Safety in patients with cardiac impairment (including congestive heart failure, current unstable angina, or left ventricular ejection fraction)	*SmPC:* *Dose reduction and treatment discontinuation guidance for left ventricular dysfunction is described in Section 4.2 (Posology and method of administration).* *Section 4.4 (Special warnings and precautions for use) describes left ventricular dysfunction and states that patients with a baseline LVEF either below institutional lower limit of normal (LLN) or below 50% have not been studied.* *PL:* *Section 2 recommends talking to the doctor, pharmacist, or nurse before taking Cotellic if the patient has heart problems.*	*None proposed*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Safety in patients with pre-existing retinal pathology or risk factors for retinal vein occlusion	*SmPC: None* *PL:* *Section 2 recommends talking to the doctor, pharmacist, or nurse before taking Cotellic if the patient has an eye problem.*	*None proposed*
Safety and efficacy in patients with CNS involvement	*SmPC:* *Section 4.4 (Pharmacodynamic properties): The safety and efficacy of the combination of Cotellic and vemurafenib in patients with a BRAF V600 mutation-positive melanoma that has metastasised to the brain is currently unknown as it has not been evaluated.* *Section 5.1 (Special warnings and precautions for use): There are no data on the safety or efficacy of cobimetinib in combination with vemurafenib in patients with central nervous system metastasis or in patients with non-cutaneous malignant melanoma.*	*None proposed*
Drug-drug interactions with CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6	*SmPC: None*	*None proposed*
Use in patients < 18 years of age	*SmPC:* *Section 4.2 (Posology and method of administration): The safety and efficacy of Cotellic in children and adolescents below 18 years of age have not been established.* *Section 5.2 (Pharmacokinetic properties): No studies have been conducted to investigate the pharmacokinetics of cobimetinib in paediatric patients.*	*None proposed*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in pregnancy and lactation	*SmPC:* *Contraceptive methods are described in Section 4.6 (Fertility, pregnancy and lactation): Women of childbearing potential should be advised to use two effective contraceptive methods, such as a condom or other barrier method (with spermicide, if available) during treatment with Cotellic and for at least three months following treatment discontinuation.* *Section 4.6 also states that Cotellic should not be used during pregnancy unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the foetus. It is not known if Cotellic passes into breast milk and the doctor should discuss the benefits and risks of taking Cotellic with a patient who is breastfeeding* *Preclinical data are described in Section 5.3 (Preclinical safety data).* *PL:* *Section 2 instructs women of childbearing potential to use two effective methods of* *contraception and to tell the doctor straight away if the patient is pregnant, becomes pregnant during treatment with Cotellic, or becomes pregnant within 3 months after the last dose.* *Section 2 states that Cotellic is not recommended during*	*None proposed*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	pregnancy and may cause permanent harm or birth defects to an unborn baby. The section also recommends asking the doctor or pharmacist for advice if the patient is breastfeeding, pregnant, or could be pregnant.	

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

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

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Cotellic (COBIMETINIB) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

The pivotal study for the present application is for all practical purposes the randomised, placebo-controlled Phase III trial GO28141, “coBRIM”. The final CSR from this study was submitted on Day 121. Updated efficacy and safety analyses were also provided in responses to questions; no p-values were provided due to the exploratory nature of these analyses.

Cobimetinib is an orally available and selective small molecule inhibitor of the mitogen-activated protein kinases MEK1 and MEK2, central components of the RAS/RAF/MEK/ERK signal transduction pathway. The clinical development was based on the observation that resistance to BRAF inhibition therapy is often caused by reactivation of the MAPK/ERK pathway through activation of downstream MEK. Combination of a BRAF inhibitor, such as vemurafenib, and a MEK inhibitor, such as cobimetinib,

could therefore potentially address major mechanisms of resistance. However, the results indicate that while the occurrence of vemurafenib resistance is significantly delayed by the upfront addition of cobimetinib, preformed vemurafenib-resistance can in most cases not be overcome by the subsequent addition of cobimetinib.

Beneficial effects

The Phase III study GO28141/coBRIM was a I:I-randomised, double-blind, placebo-controlled study of vemurafenib plus placebo vs. vemurafenib plus cobimetinib in BRAF V600-mutation positive patients with unresectable melanoma previously untreated for locally advanced or metastatic disease. The study met its primary endpoint with a hazard ratio (HR) for investigator-based PFS (with stratifications) of 0.51 (95% CI 0.39, 0.68; log-rank p<0.0001) in favour of the cobimetinib plus vemurafenib arm. An updated PFS analysis performed at an event rate of 65% and with data cut-off 8 months after the primary analysis showed a HR= 0.58 (95% CI: 0:46; 0.72), with a difference in medians PFS across treatment arms of 5.0 months (12.25 vs. 7.2 months) in favour of the combination therapy.

The planned interim analysis showed OS HR=0.645 (stratified analysis, p=0.05) and 0.62 (unstratified analysis, p=0.03) in favour of the cobimetinib plus vemurafenib arm. The event rate at the time of the pre-planned interim analysis was 17%. However, the results did not cross the pre-specified boundary for statistical significance. A consistent HR was observed in the updated OS analysis: 0.650 (stratified), with narrower confidence intervals than in the primary analysis. This analysis was performed at an event rate of 38%, and is considered supportive but still immature at this stage.

The confirmed ORR was 69.6% (95% CI: 63.5%, 75.3%) versus 50.0% (95% CI: 43.6%, 56.4%), respectively, i.e. a difference of 20%. Complete response was observed in 16% of patients in the cobimetinib plus vemurafenib arm and 11% of patients in the placebo plus vemurafenib arm. The median duration of response in patients treated with cobimetinib + vemurafenib was not reached at the time of the clinical cut-off in May 2014, (95% CI: 9.3 months, not estimable) and an updated analysis has not been provided. In the placebo + vemurafenib arm, the median duration of response was 7.3 months (95% CI: 5.8 months, not estimable). It should be noted that the median duration of follow-up for all patients in the study was 7.3 months.

Patient-reported outcomes (PROs) indicated no detrimental impact by cobimetinib plus vemurafenib treatment on global health status/health-related quality of life (HRQoL). Generally numerically higher responder rates were observed for cobimetinib plus vemurafenib compared with placebo plus vemurafenib, but differences were generally small, indicating similarity in HRQoL between the two treatment arms.

Subgroup analyses were consistent with the overall results, with nearly all HR point estimates below 1.0 and near the overall HR of 0.51.

In the Phase 1b study NO25395/BRIM7 of cobimetinib + vemurafenib, the median follow-up time was 9.5 months. In the BRAFi-naïve patient group (n=63), the (confirmed) objective response rate was 87%, including a complete response in 10% of patients. The median duration of response was 12.5 months. The objective response rate in the vemurafenib-progressed patients was 15% (95% CI: 7.5, 25.5); with median duration of response in responding patients at 6.7 months whereas for BRAFi-naive patients, ORR was 84.6% (95%CI: 69.9, 93.1) with a median duration of response of 11.3 months.

Uncertainty in the knowledge about the beneficial effects

In the phase III study GO28141/coBRIM, the efficacy of cobimetinib was primarily investigated in patients that were naïve to BRAF inhibitor treatment. Therefore, most of the data in patients previously

treated with BRAF inhibitors is derived from the phase 1b study NO25395/BRIM7, where half of the patients enrolled had progressed after vemurafenib treatment. The activity of the cobimetinib + vemurafenib combination in patients who had progressed on prior vemurafenib therapy was low, with ORR around 15% overall (n=66), and 26% in patients receiving the intended dose (n=27). Thus, it appears that the combination treatment did not overcome the resistance to BRAF inhibitor therapy as the response was low. Therefore, a warning has been included in section 4.4 of the SmPC that there is limited data in patients that have progressed following BRAF inhibitor therapy and that other treatment options should be considered before treatment with the combination in this prior BRAF inhibitor treated population. The sequence of treatments following progression on a BRAF inhibitor therapy has not been established.

A key exclusion criterion for study GO28141 was the exclusion of patients with active CNS metastasis. Patients with treated CNS lesions and no evidence of progression could be included. As a result, only 3 patients with CNS lesions were treated (2 in combination group, 1 in control group). A warning that the efficacy and safety of combination therapy in the treatment of brain metastases has not been studied and that the intracranial activity of cobimetinib is currently unknown has been included in section 4.4.

Risks

Unfavourable effects

The most common AEs that occurred with higher frequency in the cobimetinib plus vemurafenib arm of the pivotal study GO28141, compared with the placebo plus vemurafenib arm, include diarrhoea (56.7% vs. 28.0%), nausea (39.0% vs. 23.8%), blood creatine phosphokinase increased (29.9% vs. 2.9%), photosensitivity reaction (28.3% vs. 15.9%), aspartate aminotransferase (AST) increased (22.0% vs. 12.6%), and vomiting (21.3% vs. 12.1%). Common AEs that occurred with higher frequency in the placebo plus vemurafenib arm than in the cobimetinib plus vemurafenib arm include arthralgia (40.2% vs. 32.7%), alopecia (29.3% vs. 13.8%), and hyperkeratosis (28.5% vs. 10.2%).

In the cobimetinib monotherapy study MEK4592g the most frequent AEs among all subjects were diarrhoea (67.0%), fatigue (50.4%), rash (49.6%), nausea, vomiting (33.9% each), oedema peripheral (28.7%), abdominal pain (24%) and constipation (21%).

The most common Grade ≥ 3 AEs that occurred at a higher frequency in patients treated with placebo plus vemurafenib, compared with patients treated with cobimetinib plus vemurafenib, were, respectively, squamous cell carcinoma of the skin (11.3% vs. 2.4%), keratoacanthoma (7.5% vs. 0.8%), arthralgia (5.0% vs. 2.4%), myalgia (2.5% vs. 0.4%), and hyperkeratosis (2.1% vs. 0%).

Several important identified risks have been identified. Cases of serous retinopathy have been reported in patients treated with cobimetinib (SmPC section 4.4.) For patients reporting new or worsening visual disturbances, an ophthalmologic examination is recommended. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation (SmPC section 4.2) (SmPC section 4.8). Decrease in LVEF from baseline has been reported in patients receiving cobimetinib (SmPC section 4.4). LVEF should be evaluated before initiation of treatment to establish baseline values, then after the first month of treatment and at least every 3 months or as clinically indicated until treatment discontinuation. Decrease in LVEF from baseline can be managed using treatment interruption, dose reduction or with treatment discontinuation (see SmPC section 4.2). Photosensitivity has been observed with a higher frequency in the cobimetinib plus vemurafenib vs placebo plus vemurafenib arm (41% vs 31%). The majority of events were Grades 1 or 2, with Grade ≥3 events occurring in 3% of patients in the cobimetinib plus vemurafenib arm vs 0% in the placebo plus vemurafenib arm. This risk will be managed through recommendations in the SmPC section 4.2 for dose interruptions of both cobimetinib and vemurafenib.

Cases of Grade ≥3 and serious diarrhoea have been reported in patients treated with Cotellic. Diarrhoea should be managed with antidiarrhoeal agents and supportive care (SmPC section 4.4).

There were several important potential risks (rhabdomyolysis, serious hepatotoxicity, impaired female fertility, teratogenicity and developmental toxicity) that have been identified in the RMP. These will be managed through SmPC recommendations in the SmPC (section 4.2, 4.6 and 4.8) and through routine pharmacovigilance.

Uncertainty in the knowledge about the unfavourable effects

There were several missing information that have been included as part of the RMP. The long term safety of cobimetinib will be evaluated on an ongoing basis as part of the PSURs.

Further information on safety in patients with moderate and severe hepatic impairment will be provided by the submission of PK/ Safety study GP29342, in subjects with mild, moderate or severe hepatic impairment compared to healthy subjects, (See RMP). Currently, the risk will be managed through dose reduction and treatment discontinuation guidance as described in the SmPC Section 4.2.

The safety in patients with cardiac impairment (including congestive heart failure, current unstable angina, or left ventricular ejection fraction <50%) will be monitored through routine pharmacovigilance (SmPC section 4.2, 4.4 and 4.8). The safety in patients with pre-existing retinal pathology or risk factors for retinal vein occlusion will be also be monitored through routine pharmacovigilance.

The safety and long-term efficacy in patients with CNS involvement will be followed up in study ML29155, a phase 2 study of cobimetinib in combination with vemurafenib in active melanoma brain metastases (coBRIM-B) to determine the safety and efficacy of cobimetinib in combination with vemurafenib in patients with active melanoma brain metastases (See RMP).

Drug-drug interactions (with CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYPC19 and CYP2D6) will be evaluated in the in vitro CYP time-dependent inhibition study (15-1983), (See RMP).

The use of cobimetinib in patients < 18 years of age will be evaluated in two pediatric studies in patients 6 months to 18 years of age, which are part of the Pediatric Investigation Plan (PIP) EMEA-001425- PIP01-13-M01 and have also been included as part of the RMP. The missing data on the use of cobimetinib in pregnancy and lactation will be monitored through routine pharmacovigilance with appropriate wording in the SmPC section 4.6.

Benefit-risk balance

Importance of favourable and unfavourable effects

The clinical benefit of cobimetinib plus vemurafenib has been demonstrated with a prolongation of PFS of approximately 5 months in locally advanced or metastatic malignant melanoma. This is considered clinically relevant for the patient. Tumour responses (70% for combination therapy vs. 50% for vemurafenib monotherapy) and the duration of response, median 12.5-13 months in BRAF inhibitor-naïve patients (in both the phase III and the Phase 1b study) and 6.7 months in the smaller fraction of BRAFi-progressed patients who responded (in the Phase 1b study), were also considered of clinical importance.

The safety of cobimetinib plus vemurafenib is considered acceptable and manageable. In addition, the percentage of patients with cutaneous squamous cell carcinoma (cuSCC) and keratoacanthoma appeared to be lower than that observed with vemurafenib treatment. The risk and the actual occurrence of cuSCC is an important additive burden for patients. Therefore the decreased incidence of such squamous cell carcinoma is considered a benefit of the combination therapy.

Benefit-risk balance

The CHMP considers that the benefits of cobimetinib and vemurafenib combination therapy in adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation outweigh the risks. Therefore, the CHMP considers that the benefit risk balance is positive.

Discussion on the benefit-risk balance

The indication for the combination of cobimetinib and vemurafenib is supported by non-clinical and clinical data that suggest that targeting the MAPK kinase pathway at two separate levels is expected to improve efficacy. The main pivotal study, GO28141, has demonstrated a clinically relevant improvement in PFS and ORR, with supportive evidence from OS analysis. The study included patients that had not been previously treated with BRAF inhibitors. For patients that had been previously treated with a BRAF inhibitor, study NO25395 included a number of patients that had progressed following vemurafenib-treatment and showed that efficacy in terms of ORR and duration of response was lower in patients that progressed following BRAF inhibitor treatment compared to in BRAF-naive treated patients. Taking into account that in clinical practice, a proportion of patients will have been previously treated with other BRAF inhibitors, the CHMP highlighted that the combination treatment may not provide the same clinical benefit in those patients as what has been observed in naïve patients enrolled in the clinical trials not previously treated with MAPK kinase pathway inhibitors and that clinical benefit has not been demonstrated in this patient population. Nevertheless, the indication was not restricted as it was considered that patients previously treated with BRAF inhibitors could still derive some benefit from the combination therapy.

New therapeutic options have been approved recently for melanoma, some targeting the immune system instead of the melanoma cancer cells. Immunotherapeutic agents such as ipilimumab, pembrolizumab and nivolumab are not thought to interfere with the RAS, RAF, MEK, ERK signalling pathway and with the BRAF mutation status. However, based on the current data and information available, no recommendation can be given over the sequencing of therapies.

The safety and tolerability of the combination therapy appears to be acceptable and manageable through SmPC recommendations, routine pharmacovigilance and implementation of RMP measures.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Cotellic in the treatment “for use in combination with vemurafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see sections 4.4 and 5.1)” is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

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

Not applicable.

New Active Substance Status

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

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